

2.81 (2H, t, J=7.3Hz), 3.09 (2H, t, J=7.3Hz), 3.69 (2H, br s),
4.39 (2H, s), 6.49 (1H, s), 9.81 (1H, s).

MS (FD) m/z: 295M⁺.

[Referential Example 341] 1-[3-(5-tert-Butoxycarbonyl-
5 4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propyl]-4-[(6-
chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 321, a
reaction was effected using 3-(5-tert-butoxycarbonyl-
4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propanal and 1-
10 [(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride
as starting materials, whereby the title compound was
obtained.

¹H-NMR (CDCl₃) δ: 1.47 (9H, s), 1.69-1.79 (2H, m),
2.36 (2H, t, J=7.3Hz), 2.49-2.54 (4H, m), 2.65-2.75 (4H, m),
15 3.10 (4H, br s), 3.67 (2H, br s), 4.37 (2H, s), 6.39 (1H, s),
7.57 (1H, dd, J=8.8, 2.0Hz), 7.78 (1H, dd, J=8.8, 2.0Hz), 7.88-
7.95 (3H, m), 8.30 (1H, s).

MS (FD) m/z: 589 (M⁺, Cl³⁵), 591 (M⁺, Cl³⁷).

[Referential Example 342] 2-Aminomethyl-5-tert-
20 butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine

In tetrahydrofuran (100 ml), 5-tert-butoxycarbonyl-2-
hydroxymethyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine
(WO94/21599) (2.10 g) was dissolved. After the addition of
triphenylphosphine (2.66 g) and phthalimide (1.15 g),
25 diethyl azodicarboxylate (1.28 ml) was added dropwise,
followed by stirring at room temperature for 5 hours. The

reaction mixture was concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 4:1), whereby a colorless solid was obtained. The resulting solid was dissolved in ethanol (40 ml), followed by the addition of hydrazine hydrate (0.39 ml). The resulting mixture was heated under reflux for 5 hours. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 25:1), whereby the title compound (448 mg, 21%) was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.42 (9H, s), 2.72 (2H, m), 3.60 (2H, m), 3.80 (2H, s), 4.32 (2H, s), 6.64 (1H, s).

MS (FD) m/z : 268 M^+ .

[Referential Example 343] 1-[N-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]carbamoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In tetrahydrofuran (100 ml), 5-tert-butoxycarbonyl-2-aminomethyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (150 mg) was dissolved. Under ice cooling, carbonyl diimidazole (136 mg) was added, followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in toluene (50 ml). Under ice cooling,

triethylamine (0.23 ml) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (356 mg) were added, followed by stirring overnight at room temperature. The reaction mixture was diluted with ethyl acetate, washed with water and saturated aqueous NaCl solution and then dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure and the residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1 to 1:1), whereby the title compound (303 mg, 89%) was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.46(9H,s), 2.70(2H,br s), 3.07(4H,t,J=4.9Hz), 3.48(4H,t,J=4.9Hz), 3.66(2H,br s), 4.36(2H,br s), 4.39(2H,d,J=5.4Hz), 4.69(1H,t,J=5.4Hz), 6.58(1H,s), 7.58(1H,dd,J=8.8,2.0Hz), 7.74(1H,dd,J=8.8,2.0Hz), 7.87-7.93(3H,m), 8.30(1H,s).

MS (FD) m/z : 604 (M^+ , Cl^{35}), 606 (M^+ , Cl^{37}).

[Referential Example 344] 1-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 319, the title compound was obtained using 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (WO94/21599) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.47(9H,s), 2.79(2H,br s), 3.12(4H,t,J=4.9Hz), 3.68(2H,br s), 3.84(4H,t,J=4.9Hz),

4.42 (2H, br s), 6.91 (1H, s), 7.59 (1H, dd, J=8.8, 2.0 Hz),
7.75 (1H, dd, J=8.8, 2.0 Hz), 7.90-7.97 (3H, m), 8.30 (1H, s).

MS (FD) m/z: 575 (M^+ , Cl^{35}), 577 (M^+ , Cl^{37}).

[Referential Example 345] 1-[(5-tert-Butoxycarbonyl-
5 4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-4-
[(6-chloronaphthalen-2-yl)sulfonyl]-2-
ethoxycarbonylpiperazine

In the same manner as in Referential Example 319, the
title compound was obtained using 5-tert-butoxycarbonyl-
10 4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid
(WO94/21599) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-
ethoxycarbonylpiperazine (WO96/10022) as starting
materials.

1H -NMR ($CDCl_3$) δ : 1.32 (3H, t, J=7.3 Hz), 1.47 (9H, s), 2.35-
15 2.46 (1H, m), 2.55-2.64 (1H, m), 2.80 (2H, br s), 3.15-
3.20 (1H, m), 3.69 (2H, br s), 3.75-3.85 (1H, m),
4.12 (2H, q, J=7.3 Hz), 4.20-4.36 (2H, m), 4.39-4.48 (3H, m),
6.96 (1H, s), 7.59 (1H, dd, J=8.8, 2.0 Hz),
7.75 (1H, dd, J=8.8, 2.0 Hz), 7.88-7.94 (3H, m), 8.32 (1H, s).

20 MS (FAB) m/z: 648 [$(M+H)^+$, Cl^{35}], 650 [$(M+H)^+$, Cl^{37}].

[Referential Example 346] 1-[(6-Chloronaphthalen-2-
yl)sulfonyl]-4-[(5-cyano-4,5,6,7-tetrahydrothieno[3,2-
c]pyridin-2-yl)carbonyl]piperazine

In ethanol, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-
25 [(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-
yl)carbonyl]piperazine hydrochloride (195 mg),

triethylamine (0.2 ml) and sodium acetate (118 mg) were suspended. Cyanogen bromide (114 mg) was added to the resulting suspension, followed by stirring at room temperature for 2 hours. To the residue obtained by concentration of the reaction mixture under reduced pressure, dichloromethane was added. The mixture was washed with water and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane : methanol = 100:1), whereby the title compound (51 mg, 28%) was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.93-2.98 (2H, m), 3.11-3.14 (4H, m), 3.49-3.55 (2H, m), 3.81-3.84 (4H, m), 4.29 (2H, s), 6.89 (1H, s), 7.59 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.75 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.90-7.94 (3H, m), 8.30 (1H, s).

MS (FAB) m/z : 501 [$(\text{M}+\text{H})^+$, Cl^{35}], 503 [$(\text{M}+\text{H})^+$, Cl^{37}].

[Referential Example 347] 1-[N-(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbamoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In benzene (10 ml), 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (WO94/21599) (283 mg) was dissolved. To the resulting solution, triethylamine (0.14 ml) and diphenylphosphoryl azide (0.21 mg) were added, followed by heating under reflux for 2 hours. After the reaction mixture was cooled to room temperature, 1-[(6-chloronaphthalen-2-

yl)sulfonyl]piperazine hydrochloride (347 mg) and triethylamine (0.28 ml) were added and the mixture was heated under reflux overnight. After cooling to room temperature, to the reaction mixture was added
 5 dichloromethane and a 3N aqueous sodium hydroxide solution. The resulting mixture was separated and aqueous layer was extracted with dichloromethane. The combined organic layer thus extracted was washed with 0.5N hydrochloric acid, a saturated aqueous solution of sodium bicarbonate and
 10 saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1 to 2:1), whereby the title compound (284 mg, 48%) was obtained.

¹H-NMR (CDCl₃) δ: 1.45(9H,s), 2.65(2H,br s), 3.10(4H,t,J=4.9Hz), 3.57(4H,t,J=4.9Hz), 3.64(2H,br s), 4.27(2H,s), 6.15(1H,br s), 7.58(1H,dd,J=8.8,2.0Hz), 7.73(1H,dd,J=8.8,2.0Hz), 7.87-7.93(3H,m), 8.28(1H,s).

20 MS (FAB) m/z: 591 [(M+H)⁺, Cl³⁵], 593 [(M+H)⁺, Cl³⁷].

[Referential Example 348] 1-[N-(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)-N-methylcarbamoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

25 In N,N-dimethylformamide (10 ml), 1-[N-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-

yl)carbamoysl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine (147 mg) was dissolved. To the resulting solution, sodium hydride (60% in oil, 22 mg) was added, followed by stirring at room temperature for 30 minutes. After methyl iodide (0.023 ml) was added to the reaction mixture and the resulting mixture was stirred at room temperature for 90 minutes, the residue obtained by the concentration of the reaction mixture under reduced pressure was added with ethyl acetate. The resulting mixture was washed with water and saturated aqueous NaCl solution and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 2:1), whereby the title compound (43 mg) was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.49(9H,s), 2.63(2H,br s), 3.01(4H,t,J=4.9Hz), 3.13(3H,s), 3.40(4H,t,J=4.9Hz), 3.67(2H,br s), 4.31(2H,s), 6.21(1H,br s), 7.58(1H,dd,J=8.8,2.0Hz), 7.72(1H,dd,J=8.8,2.0Hz), 7.88-7.95(3H,m), 8.27(1H,s).

MS (FAB) m/z : 605 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 607 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Referential Example 349] 1-[(6-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 319, the title compound was obtained using 6-tert-butoxycarbonyl-

4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylic acid (WO94/21599) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials.

¹H-NMR (CDCl₃) δ: 1.47 (9H, s), 2.84 (2H, br s), 3.19 (4H, br),
 3.72 (2H, t, J=5.4 Hz), 3.87 (2H, br s), 4.54 (2H, s), 4.63 (2H, br
 s), 7.57 (1H, dd, J=8.8, 2.0 Hz), 7.76 (1H, dd, J=8.8, 2.0 Hz), 7.87-
 7.94 (3H, m), 8.30 (1H, s).

MS (FAB) m/z: 577 [(M+H)⁺, Cl³⁵], 579 [(M+H)⁺, Cl³⁷].

[Referential Example 350] 1-[(6-tert-Butoxycarbonyl-

4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-
 [(6-chloronaphthalen-2-yl)sulfonyl]-2-
 ethoxycarbonylpiperazine

In N,N-dimethylformamide (30 ml), 6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-
 carboxylic acid (WO94/21599) (742 mg), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-ethoxycarbonylpiperazine
 hydrochloride (WO96/10022) (1.00 g) and benzotriazol-1-yloxy-tris(pyrrolidino)phosphonium hexafluorophosphate
 (PyBOP®) (1.50 g) were dissolved. Triethylamine (0.40 ml)
 was added to the resulting solution, followed by stirring
 overnight at room temperature. After the reaction mixture
 was concentrated under reduced pressure, ethyl acetate was
 added to the residue. The resulting mixture was washed
 with water and saturated aqueous NaCl solution and then,
 dried over anhydrous sodium sulfate. The residue obtained
 by distilling off the solvent under reduced pressure was

purified by chromatography on a silica gel column (hexane : ethyl acetate = 4:1), whereby the title compound (505 mg, 30%) was obtained.

¹H-NMR (CDCl₃) δ: 1.24-1.37 (3H,m), 1.47 (9H,s), 2.45-
 2.60 (1H,m), 2.62-2.71 (1H,m), 2.75-2.90 (2H,m), 3.65-
 3.94 (3H,m), 4.19-4.31 (2H,m), 4.45-4.72 (4H,m), 5.35 (1/2H,br
 s), 5.71-5.77 (1/2H,m), 6.72 (1H,br s),
 7.58 (1H,dd, J=8.8,2.0Hz), 7.77 (1H,dd, J=8.8,2.0Hz), 7.88-
 7.92 (3H,m), 8.33 (1H,s).

MS (FAB) m/z: 649 [(M+H)⁺, Cl³⁵], 651 [(M+H)⁺, Cl³⁷].

[Referential Example 351] 1-[(6-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In tetrahydrofuran (5 ml), 1-[(6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine (487 mg) was dissolved. Methanol (5 ml) and a 1N aqueous sodium hydroxide solution (3 ml) were added to the resulting solution, followed by stirring at room temperature for 4 hours. After the reaction mixture was adjusted to pH 1 to 2 by the addition of 1N hydrochloric acid, ethyl acetate was added to separate the organic layer. After drying over anhydrous sodium sulfate, the residue obtained by distilling off the solvent under reduced pressure was dissolved in tetrahydrofuran (5 ml). To the resulting solution, N-methylmorpholine (0.09 ml) and

isobutyl chloroformate (0.11 ml) were added dropwise at -20°C. After stirring at -20°C for 10 minutes, an ammonia-dichloromethane solution (0.50 ml) was added to the reaction mixture. The resulting mixture was stirred at -20°C for 10 minutes, followed by the addition of 1N aqueous hydrochloric acid solution in ethanol (10 ml). The reaction mixture was warmed up to room temperature. After the reaction mixture was concentrated under reduced pressure, the residue was dissolved in dichloroethane. The resulting solution was washed with 1N hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 100:1), whereby the title compound (317 mg, 68%) was obtained.

¹H-NMR (DMSO-d₆) δ: 1.41(9H,s), 2.39-2.86(4H,m), 3.60-3.80(4H,m), 4.25-4.34(1H,m), 4.36-4.34(1/2H,m), 4.62(2H,br s), 4.97(1/2H,br s), 5.44-5.52(1/2H,m), 6.19(1/2H,br s), 7.30-7.39(1H,m), 7.63-7.85(3H,m), 8.15(1H,d,J=8.8Hz), 8.20-8.29(2H,m), 8.48(1H,s).

MS (FAB) m/z: 620 [(M+H)⁺, Cl³⁵], 622 [(M+H)⁺, Cl³⁷].

[Referential Example 352] 1-[(6-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(E)-4-chlorostyrylsulfonyl]piperazine

In the same manner as in Referential Example 319, the

title compound was obtained using 6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylic acid (WO94/21599) and 1-[(E)-4-chlorostyrylsulfonyl]piperazine hydrochloride as starting materials.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (9H, s), 2.87 (2H, br s), 3.31 (4H, m), 3.75 (2H, br s), 3.90 (2H, br s), 4.57 (2H, br s), 4.68 (2H, s), 6.64 (1H, d, $J=15.6\text{Hz}$), 7.28-7.35 (5H, m).

MS (FAB) m/z : 553 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 555 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Referential Example 353] (3S)-1-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]-3-[(6-chloronaphthalen-2-yl)sulfonamido]pyrrolidine
10

In the same manner as in Referential Example 321, a reaction was effected using 5-tert-butoxycarbonyl-2-formyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (WO94/21599) and
15 (3S)-[(6-chloronaphthalen-2-yl)sulfonamido]pyrrolidine trifluoroacetate as starting materials, whereby the title compound was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.49 (9H, s), 1.52-1.63 (1H, m), 2.03-2.12 (1H, m), 2.19-2.27 (1H, m), 2.35-2.54 (2H, m), 2.73-2.85 (3H, m), 3.59 (1H, d, $J=13.9\text{Hz}$), 3.66 (1H, d, $J=13.9\text{Hz}$),
20 3.70 (2H, br s), 3.88-3.95 (1H, m), 4.39 (2H, s), 4.99 (1/2H, s), 5.02 (1/2H, s), 6.49 (1H, s), 7.55 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.82-7.90 (4H, m), 8.40 (1H, s).

MS (FD) m/z : 561 (M^+ , Cl^{35}), 563 (M^+ , Cl^{37}).

25 [Referential Example 354] (3S)-1-[(5-tert-Butoxycarbonyl-

4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-3-
[(6-chloronaphthalen-2-yl)sulfonamido]pyrrolidine

In the same manner as in Referential Example 319, the
title compound was obtained using 5-tert-butoxycarbonyl-
4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid
(WO94/21599) and (3S)-3-[(6-chloronaphthalen-2-
yl)sulfonamido]pyrrolidine trifluoroacetate as starting
materials.

¹H-NMR (CDCl₃) δ: 1.50 (9H, s), 1.80-2.08 (2H, m), 2.75 (2H, br
s), 3.48-3.87 (6H, m), 3.88-4.05 (1H, m), 4.37 (2H, br s),
6.09 (1H, br s), 7.05-7.15 (1H, m), 7.55 (1H, dd, J=8.8, 1.5 Hz),
7.79-7.91 (4H, m), 8.41 (1H, s).

MS (FAB) m/z: 576 [(M+H)⁺, Cl³⁵], 578 [(M+H)⁺, Cl³⁷].

[Referential Example 355] (3S)-3-[[5-tert-Butoxycarbonyl-
4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methylamino]-
1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine

In the same manner as in Referential Example 321, a
reaction was effected using 5-tert-butoxycarbonyl-2-formyl-
4,5,6,7-tetrahydrothieno[3,2-c]pyridine (WO94/21599) and
(3S)-3-amino-1-[(6-chloronaphthalen-2-
yl)sulfonyl]pyrrolidine as starting materials, whereby the
title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.48 (9H, s), 1.60-1.69 (1H, m), 1.95-
2.05 (1H, m), 2.72 (2H, br s), 3.11 (1H, dd, J=10.3, 4.4 Hz), 3.30-
3.46 (4H, m), 3.68 (2H, br s), 3.72 (2H, s), 4.36 (2H, s),
6.44 (1H, s), 7.56 (1H, dd, J=8.8, 2.0 Hz), 7.86-7.91 (4H, m),

8.36 (1H, s).

MS (FD) m/z: 561 (M^+ , Cl^{35}), 563 (M^+ , Cl^{37}).

[Referential Example 356] (3S)-3-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonylamino]-
5 1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine

In the same manner as in Referential Example 319, the title compound was obtained using 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (WO94/21599) and (3S)-3-amino-1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine as starting materials.
10

1H -NMR ($CDCl_3$) δ : 1.48 (9H, s), 1.90-2.00 (1H, m), 2.11-2.22 (1H, m), 2.80 (2H, br s), 3.32-3.42 (1H, m), 3.44-3.57 (3H, m), 3.71 (2H, br s), 4.38 (2H, d, $J=1.5$ Hz), 4.40-4.49 (1H, m), 5.80-5.87 (1H, m), 6.96 (1H, s),
15 7.54 (1H, dd, $J=8.8, 1.5$ Hz), 7.83-7.89 (3H, m), 7.90 (1H, d, $J=8.8$ Hz), 8.37 (1H, s).

MS (FAB) m/z: 576 [$(M+H)^+$, Cl^{35}], 578 [$(M+H)^+$, Cl^{37}].

[Referential Example 357] 1-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-4-
20 [(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine

In the same manner as in Referential Example 319, the title compound was obtained using 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (WO94/21599) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine hydrochloride as starting
25 materials.

¹H-NMR (CDCl₃) δ: 1.47(9H,s), 2.01(2H,br s), 2.78(2H,br s),
 3.37-3.54(4H,m), 3.68(2H,br s), 3.78(2H,t,J=6.1Hz),
 3.86(2H,t,J=6.1Hz), 4.39(2H,s), 6.88(1H,br s),
 7.55(1H,dd,J=8.8,2.0Hz), 7.75-7.80(1H,m), 7.83-7.90(3H,m),
 8.33(1H,s).

MS (FD) m/z: 589 (M⁺, Cl³⁵), 591 (M⁺, Cl³⁷).

[Referential Example 358] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-cyanobenzofuran-2-yl)carbonyl]piperazine

In the same manner as in Referential Example 319, a
 reaction was effected using 6-cyanobenzofuran-2-carboxylic
 acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine
 hydrochloride as starting materials, whereby the title
 compound was obtained.

¹H-NMR (CDCl₃) δ: 3.21(4H,s), 3.95(4H,s),
 7.32(1H,d,J=1.0Hz), 7.55(1H,dd,J=8.3,1.0Hz),
 7.59(1H,dd,J=8.8,2.0Hz), 7.72(1H,d,J=8.3Hz),
 7.77(1H,dd,J=8.8,2.0Hz), 7.81(1H,s), 7.88-7.95(3H,m),
 8.32(1H,s).

MS (FAB) m/z: 480 [(M+H)⁺, Cl³⁵], 482 [(M+H)⁺, Cl³⁷].

[Referential Example 359] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-cyanobenzothiophen-2-yl)carbonyl]piperazine

In the same manner as in Referential Example 319, a
 reaction was effected using 5-cyanobenzothiophene-2-
 carboxylic acid and 1-[(6-chloronaphthalen-2-

yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.18(4H,s), 3.89(4H,s),
7.43(1H,d,J=2.0Hz), 7.60(1H,d,J=8.8Hz), 7.73-7.80(2H,m),
5 7.85-7.95(4H,m), 8.10(1H,s), 8.32(1H,s).

MS (FAB) m/z : 496 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 498 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Referential Example 360] 6-Methoxy-3,4-dihydroisoquinoline

In tetrahydrofuran (100 ml), 3-methoxyphenethylamine
10 (75.0 g) was dissolved. To the resulting solution, formic acid (60 ml) and acetic anhydride (108 ml) were added under ice cooling, followed by stirring overnight at room temperature. A saturated aqueous solution of sodium bicarbonate was added to the reaction mixture to separate
15 the organic layer. The organic layer was washed with saturated aqueous NaCl solution and then dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was dissolved in benzene (200 ml), followed by the dropwise
20 addition of phosphorus oxychloride (140 ml) under ice cooling. After stirring at 70°C for 15 minutes, the reaction mixture was successively added with ice and 2N hydrochloric acid. The resulting mixture was stirred for 1 hour under ice cooling. The water layer was separated from
25 the reaction mixture, neutralized with potassium carbonate and then extracted with dichloromethane. The extract was

dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column

(dichloromethane ~ dichloromethane : methanol = 100:1),

5 whereby the title compound (13.5 g, 17%) was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.72 (2H, t, $J=7.3\text{Hz}$), 3.72 (2H, t, $J=7.3\text{Hz}$), 3.83 (3H, s), 6.68 (1H, d, $J=2.4\text{Hz}$), 6.79 (1H, dd, $J=8.3, 2.4\text{Hz}$), 7.22 (1H, d, $J=8.3\text{Hz}$), 8.25 (1H, s).

MS (FAB) m/z : 162 ($\text{M}+\text{H}$) $^+$.

10 [Referential Example 361] 6-Methoxy-1,2,3,4-tetrahydroisoquinoline

In methanol (100 ml), 6-methoxy-3,4-dihydroisoquinoline (10.4 g) was dissolved. To the resulting solution, water (10 ml) and then sodium
15 borohydride (6.10 g) were added. The resulting mixture was stirred at room temperature for 15 minutes. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane, followed by washing with water. The organic layer thus separated was
20 dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 100:15), whereby the title compound (7.95 g, 76%) was obtained.

25 $^1\text{H-NMR}$ (CDCl_3) δ : 2.79 (2H, t, $J=5.9\text{Hz}$), 3.12 (2H, t, $J=5.9\text{Hz}$),

3.76(3H,s), 3.96(2H,s), 6.62(1H,s),
6.70(1H,dd,J=8.3,2.4Hz), 6.92(1H,d,J=8.3Hz).

MS (FAB) m/z: 164 (M+H)⁺.

[Referential Example 362] 6-Hydroxy-1,2,3,4-

5 tetrahydroisoquinoline hydrochloride

In dimethyl sulfide (20 ml), 6-methoxy-1,2,3,4-tetrahydroisoquinoline (7.75 g) was dissolved. Under ice cooling, aluminum chloride (19.0 g) was added to the resulting solution, followed by stirring at room
10 temperature for 3 hours. Dichloromethane and dilute hydrochloric acid were added to separate the water layer. The water layer was made basic by the addition of a saturated aqueous solution of sodium bicarbonate, followed by extraction with dichloromethane. The extract was dried
15 over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in saturated solution of hydrochloride in ethanol (100 ml). To the residue obtained by distilling off the solvent under reduced pressure, ethyl acetate was added. The solid thus
20 precipitated was collected by filtration, whereby the title compound (7.91 g, 90%) was obtained.

¹H-NMR (DMSO-d₆) δ: 3.06(2H,t,J=5.9Hz), 3.43(2H,m),
4.25(2H,s), 6.76(1H,d,J=2.0Hz), 6.83(1H,dd,J=8.3,2.0Hz),
7.15(1H,d,J=8.3Hz), 9.71(3H,br s).

25 MS (FAB) m/z: 150 (M+H)⁺.

[Referential Example 363] 2-tert-Butoxycarbonyl-6-hydroxy-

1,2,3,4-tetrahydroisoquinoline

In methanol (100 ml), 6-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (7.87 g) was dissolved. To the resulting solution, triethylamine (4.67 ml) and di-tert-butyl dicarbonate (13.95 g) were added, followed by stirring at room temperature for 3 hours. Ethyl acetate was added to the residue obtained by concentration of the reaction mixture under reduced pressure. The resulting mixture was washed with 1N hydrochloric acid, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 10:1 to 3:1), whereby the title compound (9.96 g, 94%) was obtained.

¹H-NMR (CDCl₃) δ: 1.49(9H,s), 2.75(2H,t,J=5.9Hz), 3.61(2H,t,J=5.9Hz), 4.48(2H,s), 6.25(1H,br s), 6.64(1H,d,J=2.4Hz), 6.70(1H,br s), 6.93(1H,d,J=7.8Hz).

[Referential Example 364] 2-tert-Butoxycarbonyl-6-trifluoromethanesulfonyloxy-1,2,3,4-tetrahydroisoquinoline

In pyridine (100 ml), 2-tert-butoxycarbonyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (9.96 g) was dissolved. To the resulting solution, trifluorosulfonic anhydride (8.10 ml) was added dropwise under ice cooling, followed by stirring at room temperature for 10 minutes. The reaction mixture was concentrated under reduced pressure and the residue was purified by chromatography on a silica gel

column (hexane : ethyl acetate = 10:1 to 6:1), whereby the title compound (13.47 g, 88%) was obtained as a colorless solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.49(9H,s), 2.87(2H,t,J=5.9Hz),

5 3.66(2H,t,J=5.9Hz), 4.59(2H,s), 7.06(1H,br s),

7.08(1H,d,J=8.3Hz), 7.17(1H,d,J=8.3Hz).

Elementary analysis for $\text{C}_{15}\text{H}_{18}\text{F}_3\text{NO}_5\text{S}$

Calculated: C, 47.24; H, 4.76; F, 14.94; N, 3.67; S, 8.41.

Found: C, 47.34; H, 4.72; F, 15.25; N, 3.42; S, 8.65.

10 [Referential Example 365] 2-tert-Butoxycarbonyl-6-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline

In methanol (50 ml), 2-tert-butoxycarbonyl-6-trifluoromethanesulfonyloxy-1,2,3,4-tetrahydroisoquinoline (1.34 g) was dissolved, followed by the addition of

15 triethylamine (0.73 ml), palladium (II) acetate (40 mg) and 1,3-(diphenylphosphino)propane (145 mg). Under a carbon monoxide gas stream, the resulting mixture was stirred

overnight at 70°C. The reaction mixture was concentrated under reduce pressure and the residue was purified by

20 chromatography on a silica gel column (hexane : ethyl acetate = 15:1), whereby the title compound (665 mg, 65%) was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.50(9H,s), 2.88(2H,m), 3.66(2H,br s),

3.91(3H,s), 4.62(2H,s), 7.17(1H,d,J=7.8Hz), 7.83(1H,s),

25 7.84(1H,d,J=7.8Hz).

[Referential Example 366] 1-[(2-tert-Butoxycarbonyl-

1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 319, the title compound was obtained using 2-tert-butoxycarbonyl-6-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (9H, s), 2.76 (2H, t, $J=5.4\text{Hz}$), 3.09 (4H, br), 3.60 (2H, t, $J=5.4\text{Hz}$), 3.77 (4H, br), 4.52 (2H, s), 7.12-7.25 (3H, m), 7.59 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.75 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.88-7.95 (3H, m), 8.30 (1H, s).

MS (FAB) m/z : 570 [$(\text{M}+\text{H})^+$, Cl^{35}], 572 [$(\text{M}+\text{H})^+$, Cl^{37}].

[Referential Example 367] 1-tert-Butoxycarbonyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine

In methanol (1000 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[ethoxycarbonyl]piperazine hydrochloride (W096/10022) (43.0 g) was dissolved, followed by the addition of triethylamine (17.1 ml) and di-tert-butyl dicarbonate (27.0 g). The resulting mixture was stirred at room temperature for 3 hours. The residue obtained by concentration of the reaction mixture under reduced pressure was added with ethyl acetate and the resulting mixture was washed with 1N hydrochloric acid. The organic layer thus extracted was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by

chromatography on a silica gel column (hexane : ethyl acetate = 8:1), whereby the title compound (46.0 g, 93%) was obtained as a colorless solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.24-1.32 (3H,m), 1.33-1.50 (9H,m),
5 2.37 (1H,m), 2.54 (1H,d,J=10.7Hz), 3.15-3.41 (1H,m), 3.68-
4.08 (2H,m), 4.10-4.39 (3H,m), 4.62 (1/2H,br s), 4.82 (1/2H,br
s), 7.58 (1H,dd,J=8.8,2.0Hz), 7.75 (1H,dd,J=8.8,2.0Hz), 7.87-
7.94 (3H,m), 8.31 (1H,d,J=2.0Hz).

MS (FAB) m/z : 483 [$(\text{M}+\text{H})^+$, Cl^{35}], 485 [$(\text{M}+\text{H})^+$, Cl^{37}].

10 Elementary analysis for $\text{C}_{22}\text{H}_{27}\text{ClNO}_6\text{S}$

Calculated: C, 54.71; H, 5.63; Cl, 7.34; N, 5.80; S, 6.64.

Found: C, 54.89; H, 5.42; Cl, 7.15; N, 5.76; S, 6.24.

[Referential Example 368] 1-tert-Butoxycarbonyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine-2-carboxylic acid

15 In tetrahydrofuran (40 ml), 1-tert-butoxycarbonyl-4-
[(6-chloronaphthalen-2-yl)sulfonyl]-2-
ethoxycarbonylpiperazine (23.0 g) was dissolved, followed
by the addition of ethanol (40 ml) and a 3N aqueous sodium
hydroxide solution (30 ml). The resulting mixture was
20 stirred at room temperature for 3 hours. To the reaction
mixture, 1N hydrochloric acid was added to make it acidic
and then ethyl acetate was added to separate the organic
layer. The organic layer was dried over anhydrous sodium
sulfate. The solid precipitated by distilling off the
25 solvent under reduced pressure was collected by filtration,
whereby the title compound (23.8 g, quant.) was obtained as

a colorless solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.41(1H,m), 2.59(1H,m), 3.15-3.38(1H,m),
3.70-4.08(2H,m), 4.20-4.39(1H,m), 4.72(1/2H,br s),
4.91(1/2H,br s), 7.58(1H,dd,J=8.8,J=2.0Hz),
5 7.76(1H,dd,J=8.8,2.0Hz), 7.87-7.95(3H,m), 8.34(1H,s).

Mass (FAB) m/z : 455($(\text{M}+\text{H})^+$, Cl^{35}], 457($(\text{M}+\text{H})^+$, Cl^{37}].

Elementary analysis for $\text{C}_{20}\text{H}_{23}\text{ClNO}_6\text{S}$

Calculated: C, 52.80; H, 5.10; Cl, 7.79; N, 6.16; S, 7.05.

Found: C, 52.62; H, 5.00; Cl, 7.75; N, 6.22; S, 6.83.

10 [Referential Example 369] 1-tert-Butoxycarbonyl-2-carboxymethyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 367 or
368, the title compound was obtained using 1-[(6-
15 chloronaphthalen-2-yl)sulfonyl]-3-

[methoxycarbonylmethyl]piperazine as a starting material.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.38(9H,s), 2.32(1H,dt,J=12.2,3.4Hz),
2.48(1H,dd,J=12.2,3.4Hz), 2.61(1H,dd,J=15.6,5.9Hz),
2.86(1H,dd,J=15.6,8.3Hz), 3.13(1H,s), 3.68(3H,s), 3.74-
20 4.08(3H,m), 7.58(1H,dd,J=8.8,2.0Hz),
7.74(1H,dd,J=8.8,2.0Hz), 7.89-7.94(3H,m), 8.29(1H,s).

MS (FAB) m/z : 469 [$(\text{M}+\text{H})^+$, Cl^{35}], 471 [$(\text{M}+\text{H})^+$, Cl^{37}].

Elementary analysis for $\text{C}_{22}\text{H}_{27}\text{ClN}_2\text{O}_7\text{S}$

Calculated: C, 54.71; H, 5.63; Cl, 7.34; N, 5.80; S, 6.64.

25 Found: C, 54.74; H, 5.69; Cl, 7.34; N, 5.84; S, 6.62.

[Referential Example 370] 6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine

In anhydrous tetrahydrofuran (500 ml), 6-ethoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (WO94/21599) (21.0 g) was dissolved, followed by the addition of a solution of lithium aluminum hydride in tetrahydrofuran (a 1.0M solution, 200 ml) under ice cooling. The resulting mixture was stirred at room temperature for 2 hours. Water (7 ml) was then added slowly to the reaction mixture. After the termination of the reaction, a 1N aqueous potassium hydroxide solution (7 ml) and anhydrous magnesium sulfate were successively added. After removal of the insoluble matter by filtration, the filtrate was concentrated under reduced pressure. The residue thus obtained was purified by distillation under reduced pressure (1.5 mmHg, boiling point: 82 to 85°C), whereby the title compound (6.10 g, 40%) was obtained as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.52(3H,s), 2.83(2H,t,J=5.9Hz), 2.98(2H,t,J=5.9Hz), 3.70(2H,s), 3.87(2H,br s), 8.63(1H,s).
MS (FAB) m/z : 155 $[(\text{M}+\text{H})^+]$.

[Referential Example 371] Lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate

In anhydrous tetrahydrofuran (200 ml), 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (6.43 g) was dissolved, followed by the dropwise addition of a solution

(1.47M, 34.00 ml) of n-butyl lithium in n-hexane at an external temperature of -78°C . The resulting mixture was stirred for 40 minutes without changing the temperature. Then a carbon dioxide gas was blown into the reaction mixture for 1 hour. After warming up to room temperature, the reaction mixture was concentrated under reduced pressure, whereby the title compound (9.42 g, quant.) was obtained as a pale brown foamy solid.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.37(3H,s), 2.64-2.77(4H,m),
3.54(2H,s).

MS (FAB) m/z : 199 ($\text{M}+\text{H}$) $^+$.

[Referential Example 372] N-[[1-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-3-yl]carbonyl]glycine ethyl ester trifluoroacetate

In the same manner as in Referential Example 319, an amide bond was formed using 1-tert-butoxycarbonyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine-2-carboxylic acid as a starting material, followed by deprotection using trifluoroacetic acid, whereby the title compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.20(3H,t,J=7.3Hz), 2.47-2.82(2H,m),
3.14-3.28(1H,m), 3.30-3.39(1H,m), 3.72-3.79(1H,m),
3.95(2H,d,J=5.9Hz), 4.08-4.18(3H,m),
4.20(1H,dd,J=11.2,3.4Hz), 7.75(1H,dd,J=8.8,2.0Hz),
7.84(1H,d,J=8.8Hz), 8.23(1H,d,J=8.8Hz), 8.28(1H,s),
8.30(1H,d,J=8.8Hz), 8.55(1H,s), 9.29(1H,t,J=5.9Hz).

MS (FAB) m/z : 440 $[(M+H)^+, Cl^{35}]$, 442 $[(M+H)^+, Cl^{37}]$.

[Referential Example 373] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[(morpholin-4-yl)carbonyl]methyl]piperazine hydrochloride

5 In the same manner as in Referential Example 319, an amid bond was formed using 1-tert-butoxycarbonyl-2-carboxymethyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine and morpholine as starting materials, followed by deprotection In the same manner as
10 in Referential Example 1, whereby the title compound was obtained.

1H -NMR (DMSO- d_6) δ : 2.65-2.91 (4H,m), 3.10-3.22 (1H,m), 3.30-3.82 (12H,m), 7.74 (1H,d,J=8.8Hz), 7.84 (1H,d,J=8.8Hz), 8.20 (1H,d,J=8.8Hz), 8.22-8.31 (2H,m), 8.55 (1H,s), 9.18 (1H,br
15 s), 9.32 (1H,br s).

MS (FAB) m/z : 438 $[(M+H)^+, Cl^{35}]$, 440 $[(M+H)^+, Cl^{37}]$.

[Referential Example 374] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[N-(morpholin-4-yl)carbamoyl]piperazine trifluoroacetate

20 In the same manner as in Referential Example 372, the title compound was obtained.

1H -NMR (DMSO- d_6 at 100°C) δ : 2.59-3.97 (13H,m), 4.00-4.12 (1H,m), 4.38-4.50 (1H,m), 7.68 (1H,dd,J=8.8,2.4Hz), 7.84 (1H,d,J=8.8Hz), 8.15 (1H,d,J=8.8Hz), 8.18 (1H,s),
25 8.22 (1H,d,J=8.8Hz), 8.48 (1H,s), 9.18 (1H,br s).

MS (FAB) m/z: 439 [(M+H)⁺, Cl³⁵], 441 [(M+H)⁺, Cl³⁷].

[Referential Example 375] Ethyl N'-[[1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-3-yl]carbonyl]hydrazinoacetate hydrochloride

5 In the same manner as in Referential Example 372, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.20-1.24 (3H,m), 2.55-2.90 (2H,m), 3.00-3.20 (1H,m), 3.30-3.38 (1H,m), 3.53-3.87 (3H,m), 3.94-4.19 (3H,m), 4.27 (1/2H,d,J=9.8Hz), 4.54-4.63 (1/2H,m),
10 4.95 (1H,br s), 7.75 (1H,dd,J=8.8,2.0Hz), 7.84-7.95 (1H,m), 8.19-8.32 (3H,m), 8.56 (1H,s), 8.80-9.00 (1H,m), 9.78-10.20 (1H,m).

MS (FAB) m/z: 455 [(M+H)⁺, Cl³⁵], 457 [(M+H)⁺, Cl³⁷].

[Referential Example 376] 4-(Aminoacetyl)morpholine
15 hydrochloride

In N,N-dimethylformamide (100 ml), N-tert-butoxycarbonylglycine (2.00 g), morpholine (1.00 ml), 1-hydroxybenzotriazole monohydrate (1.74 g) and 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
20 (2.84 g) were dissolved, followed by stirring overnight at room temperature. After concentration under reduced pressure, the residue was diluted with dichloromethane, washed with water and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under
25 reduced pressure was purified by chromatography on a silica gel column (dichloromethane : methanol = 100:1), whereby a

colorless foam was obtained. The substance was dissolved in dichloromethane (2 ml), followed by the addition of saturated solution of hydrochloride in ethanol (10 ml). The resulting mixture was stirred at room temperature for 5 minutes. The reaction mixture was concentrated to dryness under reduced pressure, whereby the title compound (1.80 g, quant.) was obtained as a pale yellow foam was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.39(2H,t,J=4.5Hz), 3.48(2H,t,J=4.5Hz), 3.52-3.63(4H,m), 3.77-3.90(2H,m), 8.32(3H,br s).

MS (FAB) m/z : 145 ($\text{M}+\text{H}$) $^+$.

[Referential Example 377] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[N-[(morpholin-4-yl)carbonyl]methyl]carbamoyl]piperazine hydrochloride

In the same manner as in Referential Example 372, the title compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.67(1H,d,J=11.2Hz), 2.79(1H,d,J=11.2Hz), 3.09-3.18(1H,m), 3.17-3.30(1H,m), 3.42(1H,d,J=13.2Hz), 3.45-3.74(8H,m), 3.82(1H,d,J=12.2Hz), 4.10-4.30(4H,m), 7.86(1H,d,J=8.8Hz), 7.95(1H,d,J=8.8Hz), 8.32(1H,d,J=8.8Hz), 8.40(1H,s), 8.41(1H,d,J=8.8Hz), 8.67(1H,d,J=8.8Hz), 8.93(1H,br s), 9.12(1H,d,J=4.9Hz), 10.03(1H,br s).

MS (FAB) m/z : 481 [$(\text{M}+\text{H})^+$, Cl^{35}], 483 [$(\text{M}+\text{H})^+$, Cl^{37}].

[Referential Example 378] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]piperazine

trifluoroacetate

In the same manner as in Referential Example 319, 1-tert-butoxycarbonyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine-2-carboxylic acid was reacted with methylamine to form an amide bond and then the protecting group was removed using trifluoroacetic acid, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.54-2.65 (2H, m), 2.67 (3H, d, J=3.9 Hz), 3.12-3.22 (1H, m), 3.33 (1H, d, J=13.2 Hz), 3.70 (1H, d, J=12.2 Hz), 4.04 (2H, d, J=8.8 Hz), 7.75 (1H, dd, J=8.8, 2.0 Hz), 7.87 (1H, d, J=8.8 Hz), 8.20 (1H, d, J=8.8 Hz), 8.27 (1H, s), 8.29 (1H, d, J=8.8 Hz), 8.58 (1H, s), 8.70 (1H, d, J=4.4 Hz), 9.06 (1H, br s).

MS (FAB) m/z: 440 [(M+H)⁺, Cl³⁵], 442 [(M+H)⁺, Cl³⁷].

In the same manner as in Referential Example 378, Compounds of Referential Examples 379 to 384 were synthesized.

[Referential Example 379] 4-[[1-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-3-yl]carbonyl]morpholine

trifluoroacetate

¹H-NMR (DMSO-d₆) δ: 2.49-2.58 (1H, m), 2.64-2.75 (1H, m), 3.09-3.81 (11H, m), 3.93 (1H, d, J=12.2 Hz), 4.76 (1H, dd, J=10.7, 2.4 Hz), 7.75 (1H, d, J=8.8 Hz), 7.90 (1H, d, J=8.8 Hz), 8.21 (1H, d, J=8.8 Hz), 8.27 (1H, s), 8.29 (1H, d, J=8.8 Hz), 8.58 (1H, s), 9.15 (1H, br s).

MS (FAB) m/z: 440 [(M+H)⁺, Cl³⁵], 442 [(M+H)⁺, Cl³⁷].

[Referential Example 380] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[(N-tert-butoxy)carbonyl]piperazine trifluoroacetate

¹H-NMR (DMSO-d₆) δ: 2.58-2.70 (2H,m), 3.14-3.23 (1H,m), 3.30-3.40 (1H,m), 3.64 (1H,d,J=12.2Hz), 3.97 (1H,d,J=12.2Hz), 4.05 (1H,dd,J=10.2,3.4Hz), 7.74 (1H,dd,J=8.8,2.0Hz), 7.87 (1H,d,J=8.8Hz), 8.21 (1H,d,J=8.8Hz), 8.27 (1H,d,J=2.0Hz), 8.29 (1H,d,J=8.8Hz), 8.57 (1H,s), 11.24 (1H,s).

MS (FAB) m/z: 426 [(M+H)⁺, Cl³⁵], 428 [(M+H)⁺, Cl³⁷].

10 [Referential Example 381] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[(N-isopropyl)carbamoyl]piperazine hydrochloride

¹H-NMR (DMSO-d₆) δ: 1.05-1.18 (6H,m), 2.60-2.77 (2H,m), 3.08-3.16 (1H,m), 3.30-3.41 (1H,m), 3.67 (1H,d,J=12.2Hz), 3.80-3.90 (1H,m), 4.99 (2H,d,J=7.8Hz), 7.74 (1H,dd,J=8.8,2.0Hz), 7.87 (1H,dd,J=8.8,1.5Hz), 8.22 (1H,d,J=8.8Hz), 8.28 (1H,s), 8.31 (1H,d,J=8.8Hz), 8.58 (1H,s), 8.74 (1H,d,J=7.3Hz).

MS (FAB) m/z: 396 [(M+H)⁺, Cl³⁵], 398 [(M+H)⁺, Cl³⁷].

20 [Referential Example 382] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[[piperidin-1-yl]carbonyl]methyl]piperazine hydrochloride

¹H-NMR (DMSO-d₆) δ: 1.45-1.90 (8H,m), 2.78 (1H,d,J=16.1Hz), 3.08-3.20 (1H,m), 3.20-3.60 (7H,m), 3.68-3.92 (3H,m), 7.58 (1H,d,J=8.8Hz), 7.71 (1H,d,J=8.8Hz), 7.85-7.98 (3H,m), 8.31 (1H,s), 9.09 (1H,br s), 11.32 (1H,br s).

25

MS (FAB) m/z: 436 [(M+H)⁺, Cl³⁵], 438 [(M+H)⁺, Cl³⁷].

[Referential Example 383] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[[N-(2-methoxybenzyl)]carbamoyl]piperazine hydrochloride

5 ¹H-NMR (DMSO-d₆) δ: 2.69(1H,t,J=11.2Hz), 2.72-2.30(1H,m),
3.08-3.16(1H,m), 3.31-3.37(1H,m), 3.68(1H,d,J=12.2Hz),
4.05(1H,d,J=12.2Hz), 4.14(1H,dd,J=10.3,3.4Hz),
4.29(1H,d,J=5.4Hz), 6.93(1H,t,J=7.3Hz), 7.02(1H,d,J=7.8Hz),
7.24(1H,d,J=7.3Hz), 7.29(1H,t,J=7.8Hz),
10 7.77(1H,dd,J=8.8,2.0Hz), 7.88(1H,d,J=8.8Hz),
8.23(1H,d,J=8.8Hz), 8.30(1H,s), 8.32(1H,d,J=8.8Hz),
8.59(1H,s), 9.17(1H,t,J=5.4Hz).

MS (FAB) m/z: 474 [(M+H)⁺, Cl³⁵], 476 [(M+H)⁺, Cl³⁷].

[Referential Example 384] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[N-(2-methoxyethyl)]carbamoyl]piperazine

15 ¹H-NMR (DMSO-d₆) δ: 2.54-2.75(2H,m), 3.02-3.51(7H,m),
3.70(1H,d,J=12.2Hz), 7.75(1H,d,J=8.8Hz),
7.87(1H,d,J=8.8Hz), 8.22(1H,d,J=8.8Hz), 8.28(1H,s),
8.31(1H,d,J=8.8Hz), 8.58(1H,s), 8.97(1H,t,J=5.4Hz),
20 10.01(1H,br s).

MS (FAB) m/z: 412 [(M+H)⁺, Cl³⁵], 414 [(M+H)⁺, Cl³⁷].

[Referential Example 385] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[carbamoylmethyl]piperazine hydrochloride

In N,N-dimethylformamide (20 ml), 1-tert-
25 butoxycarbonyl-2-carboxymethyl-4-[(6-chloronaphthalen-2-

yl)sulfonyl]piperazine (800 mg) was dissolved, followed by the addition of pyridine (0.85 ml), ammonium bicarbonate (417 mg) and di-tert-butoxy carbonate (1.15 g). The resulting mixture was stirred at room temperature for 7 hours. After concentration of the reaction mixture under reduced pressure, the residue was added with dichloromethane, washed with 1N hydrochloric acid and a saturated aqueous solution of sodium bicarbonate, each once and then dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. After the addition of saturated aqueous hydrochloric acid in ethanol (30 ml) to the residue, the resulting mixture was concentrated under reduced pressure. While washing with ethanol, the solid thus precipitated was removed by filtration. The filtrate was then concentrated under reduced pressure. The residue was crystallized in methanol, whereby the title compound (426 mg) was obtained as a colorless solid.

IR(KBr)cm⁻¹: 3185, 2917, 2684, 2607, 1677, 1342, 1299, 1170, 1155, 1135, 755, 692, 578.

¹H-NMR (DMSO-d₆) δ: 2.58-2.65(1H,m), 2.72-2.83(1H,m), 3.12-3.21(1H,m), 3.30-3.48(3H,m), 3.55-3.81(1H,m), 7.21(1H,br s), 7.66(1H,br s), 7.73(1H,dd,J=8.8,2.0Hz), 7.85(1H,d,J=8.8Hz), 8.20(1H,d,J=8.8Hz), 8.26(1H,s), 8.29(1H,d,J=8.8Hz), 8.56(1H,s), 9.02-9.23(2H,m).

MS (FAB) m/z: 368 [(M+H)⁺, Cl³⁵], 370 [(M+H)⁺, Cl³⁷].

[Referential Example 386] 1-(3-Furyl)-2-nitroethylene

To a solution of 3-furaldehyde (10.0 g) in ethanol (200 ml), nitromethane (6.37 g) was added at room temperature, followed by the dropwise addition of a 10N-
5 aqueous sodium hydroxide solution (11.0 ml) at 0°C. The resulting mixture was stirred for 1 hour. The reaction mixture was poured into a 15% aqueous solution of hydrochloric acid (500 ml). The precipitate so formed was collected by filtration and dried, whereby the title
10 compound (8.01 g) was obtained as a yellowish white solid. ¹H-NMR (CDCl₃) δ: 6.57(1H,d,J=2.0Hz), 7.39(1H,d,J=13.4Hz), 7.52(1H,br s), 7.83(1H,br s), 7.94(1H,d,J=13.4Hz).

[Referential Example 387] 2-(t-Butoxycarbonylamino)-1-(3-furyl)ethane

15 In tetrahydrofuran (170 ml), lithium aluminum hydride (2.20 g) was suspended, followed by the dropwise addition of a solution of 1-(3-furyl)-3-nitroethylene (8.00 g) in tetrahydrofuran (80 ml) at room temperature over 2 hours. The resulting mixture was stirred for 30 minutes. After
20 the reaction mixture was cooled to 0°C, ethyl acetate (50 ml) and then water (10 ml) were dropwise added thereto. The mixture was stirred while gradually warmed up. The reaction mixture was subjected to Celite filtration by using ethyl acetate. After the filtrate was concentrated,
25 the residue was dissolved in methylene chloride (200 ml). Di-t-butyl dicarbonate (12.6 g) was added to the resulting

solution at room temperature and the mixture was stirred for 1 hour. The reaction mixture was concentrated and the residue was purified by chromatography on a silica gel column (400 g of silica gel, hexane : ethyl acetate = 15:1 → 8:1), whereby the title compound (4.30 g) was obtained as a pale yellow transparent oil.

¹H-NMR (CDCl₃) δ: 1.44(9H,s), 2.61(2H,t,J=6.8Hz), 3.25-3.37(2H,m), 4.57(1H,br s), 6.29(1H,s), 7.26(1H,s), 7.37(1H,s).

[Referential Example 388] 6-(t-Butoxycarbonyl)-4,5,6,7-tetrahydrofuro[2,3-c]pyridine

Paraformaldehyde (625 mg) and p-toluenesulfonic acid (49.5 mg) were added to a solution of 2-(t-butoxycarbonylamino)-1-(3-furyl)ethane (2.20 g) in toluene (300 ml), followed by heating under reflux for 2 hours while dehydrating using a Dean Stark apparatus. After the reaction mixture was allowed to cool down to room temperature, a saturated aqueous solution (200 ml) of sodium bicarbonate and ethyl acetate (200 ml) were added to the reaction mixture to cause separation. The water layer was extracted with ethyl acetate (100 ml). The organic layers were combined, washed with saturated aqueous NaCl solution (100 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (100 g of silica gel, hexane : ethyl acetate = 15:1 → 10:1), whereby

the title compound (1.04 g) was obtained as a white solid.

IR(KBr) cm^{-1} :

3145, 3005, 2976, 2925, 2862, 1695, 1448, 1419, 1365, 1279, 1228, 1165, 1124, 912, 895, 758.

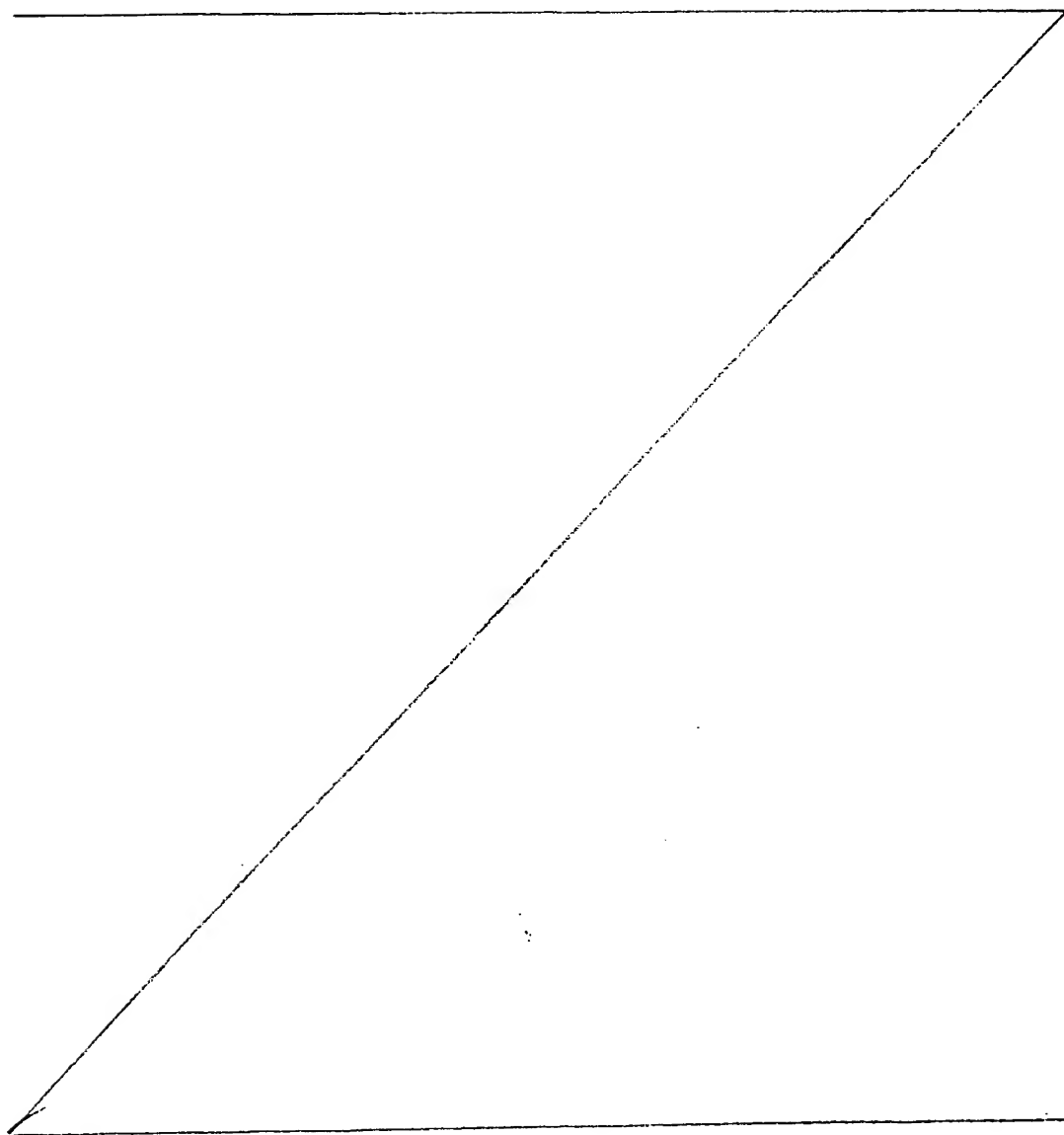
5 ^1H -NMR (CDCl_3) δ : 1.48(9H,s), 2.52(2H,br s), 3.63(2H,br s), 4.44(2H,s), 6.25(1H,s), 7.29(1H,s).

MS (FAB) m/z : 224 $[(\text{M}+\text{H})^+]$, 168 $[(\text{M}+\text{H}-\text{isobutene}(56))^+]$.

[Referential Example 389] 6-Methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridine

10 To 6-(t-butoxycarbonyl)-4,5,6,7-tetrahydrofuro[2,3-c]pyridine (1.05 g), a saturated solution of hydrochloride in ethanol (30 ml) was added at room temperature. After stirring for 2 hours, the reaction mixture was concentrated. The residue thus obtained was suspended in
15 methylene chloride (20 ml), followed by the addition of methanol (20 ml), triethylamine (1.31 ml), acetic acid (810 μl), formaldehyde (a 37% aqueous solution, 610 μl) and sodium triacetoxyborohydride (1.51 g) at room temperature. The resulting mixture was stirred for 1 hour. To the
20 reaction mixture, a saturated aqueous solution (100 ml) of sodium bicarbonate and methylene chloride (20 ml) were added to cause separation. The water layer was extracted with methylene chloride (3 x 10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and
25 concentrated under reduced pressure. The residue thus

obtained was purified by chromatography on a silica gel column (50 g of silica gel, methylene chloride : acetone = 1:1 → 1:2 → methylene chloride : methanol = 10:1), whereby the title compound (434 mg) was obtained as a
5 colorless transparent oil.



^1H -NMR (CDCl_3) δ : 2.48 (3H, s), 2.56 (2H, t, $J=5.6\text{Hz}$),
2.67 (2H, t, $J=5.6\text{Hz}$), 3.48 (2H, s), 6.23 (1H, d, $J=2.0\text{Hz}$),
7.25 (1H, s).

[Referential Example 390] 3-Aminoacrylaldehyde

5 To a solution of isoxazole (5.00 g) in methanol (100 ml), Raney nickel ("R-100", product of Nikko Chemical) (about 1.0 g) was added at room temperature. Under a hydrogen atmosphere ($3.05 - 2.65 \text{ kg/cm}^2$), the resulting mixture was stirred for 3 hours. The reaction mixture was
10 subjected to Celite filtration and the filtrate was concentrated. The residue thus obtained was reprecipitated in a chloroform - hexane system, whereby the title compound (4.91 g, 69.1 mmol, 95%) was obtained as a yellow solid.

^1H -NMR (CDCl_3) δ : 4.60-5.20 (2H, br),
15 5.45 (1H, dd, $J=12.7, 8.3\text{Hz}$), 7.15 (1H, d, $J=12.7\text{Hz}$),
9.18 (1H, d, $J=8.3\text{Hz}$).

^1H -NMR (CD_3OD) δ : 5.55 (1H, dd, $J=12.2, 9.3\text{Hz}$),
7.59 (1H, d, $J=12.2\text{Hz}$), 8.98 (1H, d, $J=9.3\text{Hz}$).

[Referential Example 391] 6-(t-Butoxycarbonyl)-5,6,7,8-
20 tetrahydro-1,6-naphthylidine

Triethylamine (1.50 ml) and pyridinium acetate (30.0 mg) were added to 1-benzyl-4-piperidone (3.80 g) and 3-aminoacrylaldehyde (2.10 g), followed by stirring under heat at 120°C . After 22 hours, the reaction mixture was
25 allowed to cool down to room temperature and the brown

caramel-like substance thus obtained was dissolved in a 3N aqueous solution of hydrochloric acid. The resulting solution was extracted with chloroform (2 x 50 ml). To the water layer, a saturated aqueous solution (50 ml) of sodium bicarbonate was added, followed by extraction with chloroform (3 x 60 ml). The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was distilled (0.90 mmHg, 145 to 150°C), whereby about 3:2 mixture (1.98 g) of 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthylidene in the form of a pale yellow transparent oil and 1-benzyl-4-piperidone as the starting material was obtained.

The mixture was dissolved in acetic acid (25 ml). To the resulting solution, 10% palladium-carbon (500 mg) was added, followed by vigorous stirring at 50 to 60°C under a hydrogen atmosphere (about 1 atm). After the stirring was continued for 2 hours, the reaction mixture was allowed to cool down and filtered. By the concentration of the filtrate, a residue containing 5,6,7,8-tetrahydro-1,6-naphthylidene in the form of a colorless transparent oil was obtained.

The residue was dissolved in toluene (20 ml), followed by the addition of a 40% aqueous solution of sodium hydroxide (30 ml) and di-*t*-butyl dicarbonate (3.20 g, 14.7 mmol) at room temperature. After stirring for 10 minutes, water (30 ml) and toluene (20 ml) were added to the

reaction mixture to cause separation. The water layer was extracted with toluene (30 ml). The organic layers were combined, washed with saturated aqueous NaCl solution (50 ml), dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (50 g of silica gel, methylene chloride : ethyl acetate = 5:1 → 3:1), whereby the title compound (981 mg) was obtained as a colorless transparent oil.

IR(KBr)cm⁻¹: 2974, 1693, 1577, 1454, 1419, 1392, 1365, 1288, 1259, 1241, 1228, 1161, 1119, 1097, 989, 930, 881, 862, 789, 768, 737.

¹H-NMR (CDCl₃) δ: 1.50(9H,s), 3.01(2H,t,J=5.9Hz), 3.76(2H,t,J=5.9Hz), 4.59(2H,s), 7.13(1H,dd,J=7.8,4.9Hz), 7.41(1H,d,J=7.8Hz), 8.43(1H,d,J=4.9Hz).

MS (FAB) m/z: 235 [(M+H)⁺], 179 [(M+H)⁺-isobutene(56)].

[Referential Example 392] 6-(t-Butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthylidin-1-oxide

To a solution of 6-(t-butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthylidine (1.72 g) in methylene chloride (40 ml), metachloroperbenzoic acid (3.80 g) was added at 0°C and the resulting mixture was stirred. Thirty minutes later, dimethyl sulfide (1.62 ml) was added to the reaction mixture, followed by stirring at room temperature for 30 minutes. To the reaction mixture, a saturated aqueous

solution (150 ml) of sodium bicarbonate and methylene chloride (30 ml) were added to cause separation. The water layer was extracted with methylene chloride (3 x 30 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue thus obtained was purified by chromatography on a silica gel column (100 g of silica gel, methylene chloride : methanol = 20:1 → 10:1), whereby the title compound (1.80 g, 7.19 mmol, 98%) was obtained as a colorless transparent oil.

IR(KBr)cm⁻¹: 2976, 2929, 2860, 1697, 1431, 1365, 1263, 1240, 1167, 1115, 1028, 910, 771.

¹H-NMR (CDCl₃) δ: 1.49(9H,s), 3.05(2H,t,J=5.9Hz), 3.75(2H,t,J=5.9Hz), 4.59(2H,s), 7.04(1H,d,J=8.8Hz), 7.14(1H,dd,J=8.8,5.9Hz), 8.18(1H,d,J=5.9Hz).

[Referential Example 393] 6-(t-Butoxycarbonyl)-2-cyano-5,6,7,8-tetrahydro-1,6-naphthylidene

To a solution of 6-(t-butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthylidin-1-oxide (760 mg) in methylene chloride (15 ml), trimethylsilyl cyanide (610 μl) was added at room temperature and the resulting mixture was stirred for 5 minutes. To the reaction mixture, N,N-dimethylcarbamoyl chloride (420 μl) was added, followed by stirring for 41 hours. To the reaction mixture, a saturated aqueous solution (50 ml) of sodium bicarbonate

and chloroform (30 ml) were added to cause separation. The water layer was extracted with chloroform (30 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue thus obtained was purified by chromatography on a silica gel column (50 g of silica gel, methylene chloride : ethyl acetate = 6:1 → 2:1), whereby the title compound (697 mg) was obtained as a white solid. The resulting white solid was recrystallized from a hexane - methylene chloride system, whereby colorless needle-like crystals were obtained.

IR(KBr)cm⁻¹: 2978, 2933, 2235, 1693, 1685, 1572, 1477, 1458, 1415, 1365, 1267, 1238, 1169, 1161, 1124, 1097, 935, 839, 768.

¹H-NMR (CDCl₃) δ: 1.50(9H,s), 3.05(2H,t,J=5.9Hz), 3.77(2H,t,J=5.9Hz), 4.67(2H,s), 7.54(2H,s).

MS (FAB) m/z: 260 [(M+H)⁺], 204 [(M+H)⁺-isobutene(56)].

Elementary analysis for C₁₄H₁₇N₃O₂

Calculated: C, 64.85; H, 6.61; N, 16.20.

Found: C, 64.89; H, 6.60; N, 16.57.

[Referential Example 394] 6-(t-Butoxycarbonyl)-2-methoxycarbonyl-5,6,7,8-tetrahydro-1,6-naphthylidine

To a solution of 6-(t-butoxycarbonyl)-2-cyano-5,6,7,8-tetrahydro-1,6-naphthylidine (1.25 g) in methanol (40 ml), concentrated hydrochloric acid (40 ml) was added at room

temperature and the resulting mixture was stirred at 100°C for 3 hours. After the reaction mixture was allowed to cool down to room temperature, it was gradually poured into tetrahydrofuran (150 ml) and an aqueous solution (250 ml) of sodium carbonate (40 g), which had been stirred in advance, followed by the addition of di-*t*-butyl dicarbonate (1.58 g, 7.23 mmol) at room temperature. The resulting mixture was stirred for 30 minutes. Water (200 ml) was added to the reaction mixture to cause separation. The water layer was extracted with ethyl acetate (100 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue so obtained was purified by chromatography on a silica gel column (100 g of silica gel, methylene chloride : ethyl acetate = 3:1 → 1:1), whereby the title compound (955 mg) was obtained as a colorless oil.

¹H-NMR (CDCl₃) δ: 1.50 (9H, s), 3.12 (2H, t, J=5.9 Hz), 3.77 (2H, t, J=5.9 Hz), 4.00 (3H, s), 4.67 (2H, s), 7.57 (1H, d, J=8.1 Hz), 7.98 (1H, d, J=8.1 Hz).

[Referential Example 395] 6-(*t*-Butoxycarbonyl)-2-[[4-(chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5,6,7,8-tetrahydro-1,6-naphthylidine

To a solution of 6-(*t*-butoxycarbonyl)-2-methoxycarbonyl-5,6,7,8-tetrahydro-1,6-naphthylidine (955 mg) in tetrahydrofuran (20 ml), a 3N aqueous solution of

sodium hydroxide (20 ml) was added at room temperature.

After stirring for 2 hours, ammonium sulfate (16.0 g) was added to the reaction mixture. Concentrated hydrochloric acid was added to adjust its pH to 4, followed by

5 extraction with chloroform (2 x 20 ml). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure, whereby the residue (874 mg), that is, 6-(t-butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-

naphthylidene-2-carboxylic acid was obtained as a white

10 solid. To a solution of the resulting residue in N,N-dimethylformamide (40 ml), methylene chloride (40 ml) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

hydrochloride (1.42 g) were dissolved, followed by the addition of 1-(dimethylaminopropyl)-3-ethylcarbodiimide

15 (785 mg) and 1-hydroxybenzotriazole (555 mg) at room temperature. Then, diisopropylethylamine (1.71 ml) was added at 0°C. After stirring overnight at room

temperature, a 10% aqueous solution of citric acid (200 ml) and methylene chloride (100 ml) were added to the reaction

20 mixture to cause separation. The organic layer was

extracted with methylene chloride (50 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was

purified by chromatography on a silica gel column (100 g of
25 silica gel, methylene chloride : acetone = 10:1 → 5:1).

The white solid thus obtained was reprecipitated in a

methylene chloride - methanol - water system. After filtration and washing with water, the title compound (1.44 g) was obtained as a white solid.

IR(KBr) cm^{-1} : 2978, 2924, 2846, 1697, 1637, 1577, 1479,
 1454, 1432, 1365, 1340, 1238, 1166, 733, 577.

^1H -NMR (CDCl_3) δ : 1.50(9H, s), 2.92(2H, t, $J=5.7\text{Hz}$),
 3.11(2H, br t, $J=4.4\text{Hz}$), 3.23(2H, br t, $J=4.4\text{Hz}$),
 3.74(2H, t, $J=5.7\text{Hz}$), 3.78(2H, br t, $J=4.4\text{Hz}$), 3.90(2H, br
 t, $J=4.4\text{Hz}$), 4.59(2H, s), 7.42(1H, br d, $J=7.8\text{Hz}$), 7.47(1H, br
 d, $J=7.8\text{Hz}$), 7.58(1H, dd, $J=2.0, 8.8\text{Hz}$),
 7.77(1H, dd, $J=2.0, 8.5\text{Hz}$), 7.90(1H, d, $J=2.0\text{Hz}$), 7.92-
 7.95(2H, m), 8.30(1H, br s).

MS (FAB) m/z : 571 $[(M+H)^+, \text{Cl}^{35}]$, 515 $[(M+H)^+-\text{isobutene}(56), \text{Cl}^{35}]$.

Elementary analysis for $\text{C}_{28}\text{H}_{31}\text{ClN}_4\text{O}_5\text{S}$

Calculated: C, 58.89; H, 5.47; N, 9.81; Cl, 6.21; S, 5.61.

Found: C, 58.59; H, 5.61; N, 9.84; Cl, 6.53; S, 5.66.

[Referential Example 396] 2-(*t*-Butoxycarbonylamino)-3-(*t*-butyldiphenylsiloxy)propanol

At room temperature, imidazole (6.43 g) was added to a solution of *N*-(*t*-butoxycarbonyl)-*L*-serine methyl ester (13.8 g) in *N,N*-dimethylformamide (140 ml), followed by the addition of *t*-butyldiphenylsilyl chloride (19.7 ml) at 0°C . The resulting mixture was stirred at room temperature for 39 hours. Ethyl acetate (200 ml) and water (600 ml) were added to the reaction mixture to cause separation. The

water layer was extracted with ethyl acetate (100 ml). The organic layers were combined, washed with saturated aqueous NaCl solution (100 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus
5 obtained was dissolved in tetrahydrofuran (100 ml) and methanol (100 ml) without purification, followed by the addition of sodium borohydride (7.20 g) in portions at 0°C. After stirring at 0°C for 2 hours and then at room temperature for 1 hour, ethyl acetate (100 ml), an aqueous
10 saturated solution of ammonium chloride (300 ml) and water (300 ml) were added to the reaction mixture to cause separation. The water layer was extracted with ethyl acetate (100 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under
15 reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (500 g of silica gel, hexane : ethyl acetate = 10:1 → 1:1), whereby the title compound (24.9 g) was obtained as a white solid.

¹H-NMR (CDCl₃) δ: 1.07(9H,s), 1.44(9H,s), 2.39(1H,br s),
20 3.63-3.85(5H,m), 5.07(1H,br s), 7.35-7.48(6H,m), 7.60-7.67(4H,m).

[Referential Example 397] 2-(t-Butoxycarbonylamino)-3-(t-butyl-
diphenylsiloxy)propanal

To a solution of 2-(t-butoxycarbonylamino)-3-(t-
25 butyl-diphenylsiloxy)propanol (3.03 g) in methylene chloride (100 ml), Dess-Martin periodinane (3.60 g) was added at

room temperature. The resulting mixture was stirred for 30 minutes. To the reaction mixture, a saturated aqueous solution (50 ml) of sodium bicarbonate and a 10% aqueous solution (50 ml) of sodium sulfite were added to cause
 5 separation. The water layer was extracted with diethyl ether (50 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (150 g of silica
 10 gel, hexane : ethyl acetate = 4:1 \rightarrow 3:1), whereby the title compound (2.97 g) was obtained as a colorless transparent oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.03(9H,s), 1.46(9H,s),
 3.93(1H,dd,J=3.9,10.3Hz), 4.18(1H,d,J=2.9,10.3Hz), 4.27-
 15 4.35(1H,m), 5.33-5.43(1H,m), 7.32-7.48(6H,m), 7.55-
 7.63(4H,m), 9.66(1H,s).

[Referential Example 398] 1,5-Bis(t-butoxycarbonyl)-2-(t-butyl
 butyldiphenylsiloxy)methyl-4,5,6,7-tetrahydro-1H-
 pyrrolo[3,2-c]pyridine

20 To a solution of diisopropylamine (2.35 ml) in tetrahydrofuran (40 ml), n-butyl lithium (a 1.66 N hexane solution, 9.20 ml) was added at 0°C, followed by stirring for 30 minutes. To the reaction mixture, a solution of N-(t-butoxycarbonyl)-4-piperidone (2.77 g) in tetrahydrofuran
 25 (10 ml) was added at -78°C, and the mixture was stirred for 1.5 hours. To the reaction mixture, a solution of 2-(t-

butoxycarbonylamino)-3-(t-butyldiphenylsiloxy)propanal (2.97 g) in tetrahydrofuran (10 ml) which had been cooled to -78°C was added dropwise. The mixture was warmed up gradually and stirred for 13 hours. Water (150 ml) and diethyl ether (350 ml) were added to the reaction mixture to cause separation. The water layer was extracted with diethyl ether (100 ml). The organic layers were combined, washed with water (100 ml) and saturated aqueous NaCl solution (3 x 100 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was dissolved in methylene chloride (20 ml). Concentrated hydrochloric acid was added dropwise and the mixture was adjusted to pH 5, followed by stirring for 1 hour. Concentrated hydrochloric acid was further added dropwise to adjust its pH to 4, followed by stirring for 1 hour. A saturated aqueous solution (50 ml) of sodium bicarbonate and methylene chloride (20 ml) were added to cause separation. The water layer was extracted with diethyl ether (2 x 50 ml). The organic layers were combined, washed with saturated aqueous NaCl solution (50 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (150 g of silica gel, hexane : ethyl acetate = 8:1 → 4:1), whereby the title compound (2.20 g) was obtained as a colorless transparent caramel-like substance.

IR(KBr)cm⁻¹: 2931, 2856, 1738, 1697, 1473, 1427, 1392,
1367, 1350, 1331, 1232, 1167, 1144, 1109, 1066, 822, 739.

¹H-NMR (CDCl₃) δ: 1.08(9H,s), 1.43(9H,s), 1.49(9H,s),
2.89(2H,br s), 3.64(2H,br s), 4.32(2H,s), 4.85(2H,br s),
5 6.12(1H,s), 7.30-7.48(6H,m), 7.60-7.75(4H,m).

MS(FAB/m-NBA/NaCl) m/z: 613[(M+Na)⁺].

[Referential Example 399] 1,5-Bis(t-butoxycarbonyl)-2-
hydroxymethyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine

To a solution of 1,5-bis(t-butoxycarbonyl)-2-(t-
10 butyldiphenylsiloxy)methyl-4,5,6,7-tetrahydro-1H-
pyrrolo[3,2-c]pyridine (2.10 g) in pyridine (20 ml), a
mixture of hydrogen fluoride and pyridine was added at 0°C,
followed by stirring at room temperature for 1 hour. After
the reaction mixture was poured into ethyl acetate (50 ml)
15 and ice water (300 ml) which had been stirred in advance,
the resulting mixture was separated. The water layer was
extracted with ethyl acetate (50 ml). The organic layers
were combined, washed with a saturated aqueous solution of
sodium bicarbonate, dried over anhydrous sodium sulfate and
20 concentrated under reduced pressure. The residue thus
obtained was purified by chromatography on a silica gel
column (150 g of silica gel, hexane : ethyl acetate = 3:1),
whereby the title compound (882 mg) was obtained as a
colorless, transparent caramel-like substance.

25 IR(KBr)cm⁻¹: 3432, 2976, 2931, 1736, 1695, 1419, 1365,
1350, 1323, 1234, 1167, 1144, 1105, 754.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.47(9H,s), 1.60(9H,s), 2.85(2H,br s),
3.45-3.70(1H,br), 3.64(2H,br s), 4.29(2H,s),
4.59(2H,d, $J=7.3\text{Hz}$), 6.01(1H,s).

MS (FAB/m-NBA/NaCl) m/z : 375 $[(\text{M}+\text{Na})^+]$.

5 [Referential Example 400] 1,5-Bis(t-butoxycarbonyl)-2-
formyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine

To a solution of 1,5-bis(t-butoxycarbonyl)-2-
hydroxymethyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine
(14.0 mg) in methylene chloride (2.0 ml), Dess-Martin
10 periodinane (34.0 mg) was added at room temperature. The
resulting mixture was stirred for 1 hour. To the reaction
mixture, ethyl acetate (10 ml), a 10% aqueous solution (10
ml) of sodium thiosulfate and an aqueous solution (10 ml)
of sodium bicarbonate were added to cause separation. The
15 water layer was extracted with ethyl acetate (10 ml). The
organic layers were combined, dried over anhydrous sodium
sulfate and concentrated under reduced pressure. The
residue thus obtained was purified by thin-layer
preparative chromatography on silica gel (hexane : ethyl
20 acetate = 2:1), whereby the title compound (9.8 mg) was
obtained as a colorless transparent caramel-like substance.
IR(KBr) cm^{-1} : 2976, 2933, 1741, 1697, 1660, 1479, 1413,
1367, 1346, 1298, 1281, 1234, 1165, 1146, 1103, 895, 850,
768.

25 $^1\text{H-NMR}$ (CDCl_3) δ : 1.48(9H,s), 1.63(9H,s), 2.96(2H,br

t, J=5.4Hz), 3.68 (2H, br t, J=5.4Hz), 4.37 (2H, s), 6.97 (1H, s), 10.14 (1H, br s).

MS (FAB/m-NBA) m/z: 351 [(M+H)⁺], 295 [(M+H - isobutene(56))⁺], 239 [(M+H) - 2 x isobutene (56))⁺].

5 [Referential Example 401] 1,5-Bis(t-butoxycarbonyl)-2-[[4-(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine

To a solution of 1,5-bis(t-butoxycarbonyl)-2-formyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine (44.0 mg) in
10 t-butanol (2.0 ml), 2-methyl-2-butene (150 μ l) and an aqueous solution (6.0 ml) of sodium chlorite (102 mg) and sodium dihydrogenphosphate (135 mg) were added at room temperature. After stirring for 21 hours, the reaction mixture was added with diethyl ether (10 ml) and water (10
15 ml), followed by the addition of ammonium sulfate until saturation. The resulting mixture was separated, followed by extraction with diethyl ether (10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure, whereby the
20 residue, that is, 1,5-bis(t-butoxycarbonyl)-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid was obtained as a white foamy substance. To a solution of the resulting residue in N,N-dimethylformamide (2.0 ml), methylene chloride (2.0 ml) and 1-[(6-chloronaphthalen-2-
25 yl)sulfonyl]piperazine hydrochloride (55.0 mg) were dissolved, followed by the addition of 1-

(dimethylaminopropyl)-3-ethyl carbodiimide (30.5 mg) and 1-hydroxybenzotriazole (21.5 mg) at room temperature. At 0°C, diisopropylethylamine (67.0 μ l) was added thereto.

After stirring overnight at room temperature, a 10% aqueous citric acid solution (10 ml) and methylene chloride (10 ml) were added to the reaction mixture to cause separation.

The organic layer was extracted with methylene chloride (10 ml). The organic layers were combined, dried over

anhydrous sodium sulfate and concentrated under reduced

pressure. The resulting residue was purified by thin-layer preparative chromatography on silica gel (methylene

chloride : acetone = 10:1) and the white solid thus

obtained was reprecipitated in a methylene chloride -

methanol - water system. After filtration and washing

with water, the title compound (50.0 mg) was obtained as a colorless transparent caramel-like substance.

IR(KBr) cm^{-1} : 2981, 2929, 2860, 1743, 1693, 1647, 1456, 1421, 1367, 1348, 1325, 1279, 1236, 1165, 1103, 955, 945, 729.

^1H -NMR (CDCl_3) δ : 1.32(9H,s), 1.46(9H,s), 2.83(2H,br t, $J=5.6\text{Hz}$), 3.04(2H,br), 3.17(2H,br), 3.55(2H,br), 3.62(2H,br t, $J=5.6\text{Hz}$), 3.82(2H,br), 4.25(2H,s), 5.94(1H,s), 7.59(1H,dd, $J=2.0, 8.8\text{Hz}$), 7.76(1H,dd, $J=1.7, 8.5\text{Hz}$), 7.87-7.98(3H,m), 8.30(1H,br s).

MS (FAB/m-NBA/NaCl) m/z: 681 [(M+Na)⁺], 581 [(M+Na-Boc(100))⁺], 525 [(M+Na-Boc(100)-isobutene(56))⁺].

[Referential Example 402] 1-(tert-Butoxycarbonyl)-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

To a solution of lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate (293 mg) in N,N-dimethylformamide (10 ml) were added 1-(tert-butoxycarbonyl)piperazine (294 mg), 1-hydroxybenzotriazole monohydrate (214 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (303 mg) at room temperature. After stirring for 38 hours, methylene chloride (20 ml) and water (200 ml) were added to the reaction mixture to separate it into layers. The water layer thus obtained was extracted with methylene chloride (3 x 10 ml). The organic layers were combined, washed with a saturated aqueous solution (100 ml) of sodium bicarbonate, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 2:1), whereby the title compound (300 mg) was obtained as a pale yellow viscous substance.

¹H-NMR (CDCl₃) δ: 1.48(9H,s), 2.51(3H,s), 2.83(2H,t,J=5.7Hz), 2.94(2H,t,J=5.7Hz), 3.53(4H,t,J=5.2Hz), 3.71(2H,s), 3.75(2H,br s), 4.38(2H,br s).

MS (FAB) m/z: 367 (M+H)⁺, 311 (M-isobutene + H)⁺, 267 (M-Boc + H)⁺.

[Referential Example 403] Thiazolo[4,5-c]pyridine

In formic acid (60 ml) was dissolved 3-(tert-butoxyamino)-4-mercaptopyridine (9.20 g), followed by heating under reflux for 4 hours. After the reaction mixture was concentrated under reduced pressure and a 5N aqueous solution (100 ml) of potassium hydroxide was added to the residue, the resulting mixture was extracted with ether. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. Diethyl ether was added to the residue and the solid so precipitated was collected by filtration, whereby the title compound was obtained as a colorless solid (3.97 g).

¹H-NMR (CDCl₃) δ: 7.93(1H,d,J=5.4Hz), 8.60(1H,d,J=5.4Hz), 9.07(1H,s), 9.46(1H,s).

[Referential Example 404] 5-Methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine

In N,N-dimethylformamide (80 ml) was dissolved thiazolo[4,5-c]pyridine (700 mg), followed by the addition of methyl iodide (0.65 ml). The resulting mixture was stirred under heat at 80°C for 4 hours. After concentration of the reaction mixture under reduced pressure, the residue was dissolved in water (100 ml). Sodium borohydride (583 mg) was added to the resulting

solution, followed by stirring at room temperature for 1 hour. After the addition of a saturated aqueous solution of potassium carbonate, the resulting mixture was extracted with ether. The organic layer thus extracted was dried
5 over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : methanol = 25:1), whereby the title compound (596 mg) was obtained as a colorless oil.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 2.52 (3H, s), 2.77 (2H, t, $J=5.4\text{Hz}$), 2.92-3.00 (2H, m), 3.69 (2H, t, $J=2.0\text{Hz}$), 8.61 (1H, s).

MS (FAB) m/z : 155 ($\text{M}+\text{H}$) $^+$.

[Referential Example 405] Lithium 5-methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine-2-carboxylate

15 In anhydrous tetrahydrofuran (10 ml) was dissolved 5-methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine (583 mg), followed by the dropwise addition of a hexane solution (1.54M, 2.70 ml) of n-butyl lithium at -78°C . After stirring for 10 minutes, the reaction mixture was warmed up
20 to 0°C and stirring was conducted for 30 minutes. The reaction mixture was cooled to -78°C . A carbon dioxide gas was blown into the reaction mixture for 15 minutes, followed by warming up to room temperature. The reaction mixture was concentrated under reduced pressure, whereby
25 the title compound (820 mg) was obtained as a pale brown foamy solid.

¹H-NMR (DMSO-d₆) δ: 2.38 (3H, s), 2.64 (2H, br s), 2.80 (2H, br s), 3.44 (2H, br s).

MS (FD) m/z: 199 (M+H)⁺.

[Referential Example 406] Lithium thiazolo[4,5-c]pyridine-
5 2-carboxylate

In the same manner as in Referential Example 405, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 8.07 (1H, d, J=5.4Hz), 8.48 (1H, d, J=5.4Hz), 9.22 (1H, s).

10 [Referential Example 407] 5-Isopropyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine

In the same manner as in Referential Example 404, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.16 (6H, d, J=6.8Hz), 2.80-2.92 (4H, m),
15 2.95-3.03 (1H, m), 3.83 (2H, t, J=2.0Hz), 8.60 (1H, s).

MS (FAB) m/z: 183 (M+H)⁺.

[Referential Example 408] Lithium 5-isopropyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine-2-carboxylate

20 In the same manner as in Referential Example 405, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.64 (2H, br s), 2.80 (2H, br s), 3.44 (2H, br s).

MS (FAB) m/z: 277 (M+H)⁺.

[Referential Example 409] 1-Benzoyl-3-bromo-2-methyl-4-
25 piperidone

In diethyl ether (50 ml) was suspended copper cyanide (197 mg), followed by the dropwise addition of a diethyl ether solution (1.10 mole, 4.00 ml) of methyl lithium at -78°C. The reaction mixture was warmed up to 0°C. After the reaction mixture was stirred for 10 minutes, it was cooled to -78°C again. To the reaction mixture was added dropwise a diethyl ether solution (5 ml) of N-benzoylazacyclohexa-2-en-4-one (400 mg) (Can. J. Chem., 1981, 3136-3140) at -78°C, followed by stirring for 30 minutes. After trimethylsilyl chloride (0.53 ml, 4.20 mmol) was added dropwise to the reaction mixture, the resulting mixture was warmed up to room temperature. The reaction mixture was added with a saturated aqueous solution of sodium bicarbonate. The resulting solution was then extracted with ethyl acetate. The organic layer thus extracted was washed with aqueous NaCl solution. The extract was dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was dissolved in acetone (10 ml), followed by the addition of sodium acetate (135 mg), water (2 ml) and N-bromosuccinic imide (292 mg) under ice cooling. The resulting mixture was stirred overnight at room temperature. To the reaction mixture was added an aqueous solution of sodium thiosulfate (2 moles, 10 ml). After stirring for 30 minutes, ethyl acetate was added and the organic layer was collected. The organic layer thus obtained was washed with saturated

aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by chromatography on a silica gel column (ethyl acetate : hexane = 1:3), whereby the title compound (240 mg) was obtained as a yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.39(3H,d,J=7.3Hz), 2.20-2.40(1H,m), 2.65(1H,br s), 3.18-3.58(2H,m), 4.01(1H,br s), 4.15-4.62(1/2H,m), 4.80-5.28(1/2H,m), 7.40-7.55(5H,m).

MS (FAB) m/z : 296 (M^+ , Br^{79}), 298 (M^+ , Br^{81}).

[Referential Example 410] 6-Benzoyl-7-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine

In butanol (20 ml) was dissolved 1-benzoyl-2-methyl-3-bromo-4-piperidone (240 mg), followed by the addition of thioformamide (160 mg). The resulting mixture was stirred at 100°C for 2.5 hours. After the reaction mixture was cooled to room temperature, it was subjected to Celite filtration. The filtrate was washed with a saturated aqueous solution of sodium bicarbonate and saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (ethyl acetate : hexane = 1:2), whereby the title compound (56 mg) was obtained as a yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.39(3H,d,J=5.6Hz), 2.88-3.10(2H,m), 3.41(1H,br s), 3.94(1H,br s), 5.97(1H,br s), 7.38-7.48(5H,m), 8.70(1H,s).

MS (FAB) m/z: 259 (M+H)⁺.

[Referential Example 411] 6-tert-Butoxycarbonyl-7-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine

Under ice cooling, sodium hydride (60% in oil, 270 mg) was added to butanol (70 ml), followed by stirring for 30 minutes. A butanol solution (5 ml) of 6-benzoyl-7-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (240 mg) was added to the reaction mixture. The resulting mixture was heated under reflux for 4 days. After water (5 ml) was added to the reaction mixture and the mixture was heated under reflux for 30 minutes, the reaction mixture was cooled to room temperature. To the reaction mixture was added di-tert-butyl dicarbonate (883 mg) and they were stirred at room temperature for 8 hours. The reaction mixture was concentrated under reduced pressure. To the residue were added 3N hydrochloric acid (10 ml) and ethyl acetate to separate the resulting mixture into layers. The organic layer thus collected was dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by chromatography on a silica gel column (ethyl acetate : hexane = 1:4), whereby the title compound (168 mg) was obtained as a yellow oil.

¹H-NMR (CDCl₃) δ: 1.46(3H,d,J=5.6Hz), 1.49(9H,s), 2.85-2.92(2H,m), 3.10(1H,m), 4.27-4.50(1H,m), 5.23-5.52(1H,m), 8.65(1H,s).

MS (FAB) m/z: 255 (M+H)⁺.

[Referential Example 412] Lithium 6-(tert-butoxycarbonyl)-7-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate

5 In the same manner as in Referential Example 405, the title compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.38-1.40(3H,m), 1.43(9H,s), 2.60-2.82(2H,m), 3.11(1H,br s), 4.15(1H,br s), 5.10-5.32(1H,m).
MS (FAB) m/z : 298 M^+ .

[Referential Example 413] 4-Ethoxycarbonylthiazole

10 Formamide (100 ml) was stirred under ice cooling, followed by the addition of diphosphorus pentasulfide (27.48 g) in the form of a solid. The resulting mixture was stirred overnight at room temperature. Water (200 ml) was added and then the mixture was extracted with diethyl
15 ether (8 x 200 ml). The organic layers were combined, washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby thioformamide (35.8 g) was obtained as a yellow oil. While stirring, ethyl
20 bromopyruvate (20.0 g) was added to the resulting oil. After the addition of ethanol (100 ml) to the reaction mixture, ethyl bromopyruvate (45.04 g) was added further. The resulting mixture was stirred at room temperature for 3 hours. The solvent was distilled off under reduced
25 pressure. Methylene chloride was added to the residue. The resulting mixture was washed with a saturated aqueous

solution of sodium bicarbonate and saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (42.73 g) was obtained as a brown oil.

5 ^1H -NMR (CDCl_3) δ : 1.43(3H,t,J=7.3Hz), 4.45(2H,q,J=7.3Hz), 8.26(1H,d,J=2.0Hz), 8.86(1H,d,J=2.0Hz).

MS (EI) m/z : 157 M^+ .

[Referential Example 414] 4-Formylthiazole

10 In anhydrous tetrahydrofuran (150 ml) was dissolved 4-ethoxycarbonylthiazole (15.2 g) and the resulting solution was cooled to -78°C . Diisobutylaluminum hydride (a 0.95 mole hexane solution, 102 ml) was added dropwise, followed by stirring for 1 hour at a temperature maintained at -78°C . After the addition of methanol (20 ml) and heating
15 to room temperature, the reaction mixture was subjected to Celite filtration. The precipitate so obtained was washed with tetrahydrofuran and ethyl acetate and then added to a saturated aqueous solution of ammonium chloride. The resulting mixture was extracted with methylene chloride.
20 The organic layers were combined and distilled under reduced pressure to remove the solvent. The residue was then dissolved in methylene chloride. The resulting solution was washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under
25 reduced pressure to remove the solvent, whereby the title compound (7.37 g) was obtained as a yellow solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 8.27 (1H, d, $J=2.0\text{Hz}$), 8.92 (1H, d, $J=2.0\text{Hz}$), 10.15 (1H, s).

MS (EI) m/z : 113 M^+ .

[Referential Example 415] 4-(2-Nitro-1-propenyl)thiazole

5 In isopropyl alcohol (100 ml) was dissolved 4-formylthiazole (10.9 g), followed by the addition of potassium fluoride (280 mg) and nitromethane (14.46 g). The resulting mixture was stirred at 60 to 65°C for 2 hours. The reaction mixture was then stirred overnight at
10 room temperature. The solvent was distilled off under reduced pressure. The residue was dissolved in benzene (50 ml), followed by the addition of acetic anhydride (12.29 g) and 4-(dimethylamino)pyridine (588 g). The resulting mixture was heated under reflux for 2 hours. The solvent
15 was distilled off under reduced pressure. Methylene chloride was added to the residue. The resulting mixture was washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was then dried over anhydrous sodium sulfate and distilled under reduced
20 pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 1:1), whereby the title compound (8.73 g) was obtained as vividly yellow crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.78 (3H, d, $J=0.5\text{Hz}$), 7.68 (1H, d, $J=2.0\text{Hz}$),
25 8.03 (1H, m), 8.92 (1H, d, $J=2.0\text{Hz}$).

MS (EI) m/z: 170 M⁺.

[Referential Example 416] 4-[2-[N-(tert-Butoxycarbonyl)amino]propyl]thiazole

Under ice cooling, lithium aluminum hydride (2.41 g) was suspended in anhydrous tetrahydrofuran (50 ml). An anhydrous tetrahydrofuran solution (90 ml) of 4-(2-nitro-1-propenyl)thiazole (10.8 g) was added dropwise to the resulting suspension. After stirring at the same temperature for 40 minutes, sodium sulfate 10 hydrate (15 g) was added and the resulting mixture was stirred for 45 minutes. The reaction mixture was subjected to Celite filtration. From the precipitate, an organic substance was extracted with hot methanol. The organic layers were combined and distilled under reduced pressure to remove the solvent. Methylene chloride (50 ml), sodium carbonate (3.4 g) and di-tert-butyl dicarbonate (13.86 g) were added to the residue, followed by stirring at room temperature for 2 hours. The reaction mixture was washed with water, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (Φ 4 x 20 cm, hexane : ethyl acetate = 3:1 \rightarrow 3:2), whereby the title compound (2.86 g) was obtained as a brown oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.13, 1.16 (total 3H, d each, $J=6.6, 6.4\text{Hz}$),
1.42 (9H, s), 2.91-3.09 (2H, m), 4.00-4.11 (1H, m), 5.03-
5.08 (1H, m), 7.05-7.10 (1H, m), 8.75-8.77 (1H, m).
MS (FAB) m/z : 243 ($\text{M}+\text{H}$) $^+$.

5 [Referential Example 417] 6-(tert-Butoxycarbonyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine

In ethanol (26 ml) was dissolved 4-[2-[N-(tert-butoxycarbonyl)amino]propyl]thiazole (1.07 g), followed by the addition of paraformaldehyde (90%, 2.94 g) and a 1N
10 solution (13 ml) of hydrochloride in ethanol. The resulting mixture was charged in a sealed tube and stirred at 100°C for 28 hours. During stirring, operation of cooling to room temperature, loosening the lid and thereby reducing the internal pressure of the tube was carried out
15 several times. The solvent was then distilled off under reduced pressure. To the residue were added methylene chloride (18 ml), triethylamine (2.6 ml) and di-tert-butyl dicarbonate (1.45 g), followed by stirring at room temperature for 3 hours. The reaction mixture was washed
20 with water, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by column chromatography (hexane : ethyl acetate = 4:1) using, as a carrier, silica gel, whereby the title compound (625 mg) was obtained as a pale
25 yellow solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.15 (3H, d, $J=6.8\text{Hz}$), 1.49 (9H, s),
2.77 (1H, d, $J=16.6\text{Hz}$), 3.09-3.14 (1H, m), 4.21 (1H, d, $J=16.8\text{Hz}$),
4.84 (1H, br s), 5.06 (1H, br s), 8.69 (1H, s).
MS (FAB) m/z : 255 ($\text{M}+\text{H}$) $^+$.

5 [Referential Example 418] 4-Formyl-2-(trans- β -styryl)oxazole

To a solution of 4-ethoxycarbonyl-2-(trans- β -styryl)oxazole (8.57 g) (J. Org. Chem. 1996, 61, 6496-6497) in methylene chloride (80 ml) was added dropwise
10 diisobutylaluminum hydride (a 1.0 mole hexane solution, 66.0 ml) at -78°C . After stirring for 15 minutes, methanol (11 ml) was added dropwise and the resulting mixture was warmed up to room temperature over 1 hour. The reaction mixture was then subjected to Celite filtration. The pasty
15 substance thus obtained was dissolved in ethyl acetate (200 ml) and a saturated aqueous solution (200 ml) of ammonium chloride. The resulting solution was separated into layers. The water layer was extracted with methylene chloride (2 x 100 ml). The organic layers were combined
20 and washed with a saturated aqueous solution (100 ml) of sodium bicarbonate and saturated aqueous NaCl solution (100 ml), followed by the addition of the filtrate upon Celite filtration. The resulting mixture was dried over anhydrous sodium sulfate and distilled under reduced pressure to
25 remove the solvent. The residue was purified by

chromatography on a silica gel column (methylene chloride : ethyl acetate = 5:1 → methylene chloride : methanol = 10:1), whereby the title compound (5.86 g) was obtained as colorless needle crystals.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 6.96(1H,d,J=16.6Hz), 7.35-7.45(3H,m), 7.56(2H,d,J=6.4Hz), 7.67(1H,d,J=16.6Hz), 8.26(1H,s), 9.98(1H,s).

MS (FAB) m/z : 200 ($\text{M}+\text{H}$) $^+$.

[Referential Example 419] 2-(trans- β -Styryl)-4-

10 vinyloxazole

To a solution of (methyl)triphenylphosphonium bromide (8.16 g, 22.8 mmol) in tetrahydrofuran (80 ml) was added dropwise *n*-butyl lithium (a 1.54N hexane solution, 14.2 ml) at 0°C, followed by stirring at room temperature for 30
15 minutes. The reaction mixture was cooled to 0°C again and a solution of 4-formyl-2-(trans- β -styryl)oxazole (3.64 g) in tetrahydrofuran (20 ml) was added thereto. The resulting mixture was heated to room temperature. After stirring for 2 hours, water (200 ml) and ethyl acetate (100
20 ml) were added to separate the reaction mixture into layers. The water layer was extracted with ethyl acetate (50 ml). The organic layers were combined, washed with saturated aqueous NaCl solution (100 ml), dried over anhydrous sodium sulfate and distilled under reduced
25 pressure to remove the solvent. The residue was purified

by chromatography on a silica gel column (hexane : ethyl acetate = 4:1 \rightarrow 3:1), whereby the title compound (2.84 g) was obtained as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 5.33 (1H, dd, $J=10.7, 1.5\text{Hz}$),

5 5.98 (1H, dd, $J=17.6, 1.5\text{Hz}$), 6.56 (1H, dd, $J=17.6, 10.7\text{Hz}$),
6.95 (1H, d, $J=16.6\text{Hz}$), 7.31-7.42 (3H, m), 7.49-7.56 (4H, m).

MS (FAB) m/z : 198 ($\text{M}+\text{H}$) $^+$.

[Referential Example 420] 4-(2-Hydroxyethyl)-2-(trans- β -styryl)oxazole

10 To a solution of 2-(trans- β -styryl)-4-vinyloxazole
(13.0 g) in tetrahydrofuran (500 ml) was added 9-
borabicyclo[3.3.1]nonane (a 0.5 mole tetrahydrofuran
solution, 158 ml) at 0°C. The resulting mixture was
stirred at room temperature for 15 hours. At 0°C, water
15 (10 ml), a 3N aqueous solution of sodium hydroxide (80 ml)
and aqueous hydrogen peroxide (80 ml) were successively
added dropwise to the reaction mixture, followed by
stirring at room temperature for 6 hours. Water (600 ml)
and ethyl acetate (200 ml) were added to the reaction
20 mixture to separate the reaction mixture into layers. The
water layer was extracted with ethyl acetate (200 ml). The
organic layers were combined, washed with saturated aqueous
NaCl solution (200 ml), dried over anhydrous sodium sulfate
and distilled under reduced pressure to remove the solvent.
25 The residue was purified by chromatography on a silica gel

column (hexane : ethyl acetate = 2:1 → only ethyl acetate), whereby the title compound (14.1 g) was obtained as a colorless solid.

¹H-NMR (CDCl₃) δ: 2.69 (1H, br s), 2.80 (2H, t, J=5.6 Hz), 3.90-3.97 (2H, m), 6.91 (1H, d, J=16.6 Hz), 7.30-7.42 (4H, m), 7.43-7.56 (3H, m).

MS (FAB) m/z: 216 (M+H)⁺.

[Referential Example 421] N-[2-[2-(trans-β-styryl)oxazol-4-yl]ethyl]phthalimide

To a solution of 4-(2-hydroxyethyl)-2-(trans-β-styryl)oxazole (292 mg) in tetrahydrofuran (15 ml) were added phthalimide (200 mg), triphenylphosphine (357 mg) and diethyl azodicarboxylate (214 μl) at room temperature, followed by stirring for 4 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1), whereby the title compound (447 mg) was obtained as a colorless solid.

¹H-NMR (CDCl₃) δ: 2.98 (2H, t, J=7.2 Hz), 4.03 (2H, t, J=7.2 Hz), 6.88 (1H, d, J=16.6 Hz), 7.28-7.45 (5H, m), 7.48 (2H, d, J=7.3 Hz), 7.71 (2H, dd, J=5.4, 2.9 Hz), 7.84 (2H, dd, J=5.4, 2.9 Hz).

MS (FAB) m/z: 345 (M+H)⁺.

[Referential Example 422] 4-[2-(tert-Butoxycarbonylamino)ethyl]-2-(trans-β-styryl)oxazole

To a solution of N-[2-[2-(trans- β -styryl)oxazol-4-yl]ethyl]phthalimide (6.40 g) in ethanol (150 ml) was added hydrazine monohydrate (1.50 ml) at room temperature. After stirring for 1 hour, hydrazine monohydrate (500 μ l) was added again at room temperature, followed by stirring for 2 hours. At room temperature, methylene chloride (150 ml) and a saturated aqueous solution (150 ml) of sodium bicarbonate and di-tert-butyl dicarbonate (13.4 g, 61.4 mmol) were added to the reaction mixture. After stirring for 30 minutes, the reaction mixture was separated into layers. The water layer was extracted with methylene chloride (50 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 2:1 \rightarrow 1:1), whereby the title compound (5.06 g) was obtained as a colorless solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.45(9H,s), 2.75(2H,t,J=6.6Hz), 3.46(2H,dt,J=5.9,6.6Hz), 4.92(1H,br s), 6.91(1H,d,J=16.6Hz), 7.29-7.45(4H,m), 7.48(1H,d,J=16.6Hz), 7.52(2H,d,J=7.3Hz).

MS (FAB) m/z : 315 ($\text{M}+\text{H}$) $^+$.

[Referential Example 423] 6-(tert-Butoxycarbonyl)-2-(trans- β -styryl)-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine

To a solution of 4-[2-(tert-Butoxycarbonylamino)ethyl]-2-(trans- β -styryl)oxazole (190 mg) in toluene (15 ml) were added paraformaldehyde (54.5 mg) and p-toluenesulfonic acid (7.2 mg) at room temperature. After heating under reflux for 1 hour, the reaction mixture was allowed to cool down. Ethyl acetate (15 ml) and a saturated aqueous solution (15 ml) of sodium bicarbonate were added to the reaction mixture to separate it into layers. The water layer was extracted with ethyl acetate (10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1 \rightarrow 2:1), whereby the title compound (153 mg) was obtained as a colorless transparent viscous substance. $^1\text{H-NMR}$ (CDCl_3) δ : 1.50 (9H, s), 2.67 (2H, br s), 3.73 (2H, br s), 4.55 (2H, s), 6.90 (1H, d, $J=16.1\text{Hz}$), 7.29-7.42 (3H, m), 7.46 (1H, d, $J=16.1\text{Hz}$), 7.52 (2H, d, $J=7.3\text{Hz}$). MS (FAB) m/z : 327 ($\text{M}+\text{H}$) $^+$.

[Referential Example 424] 6-(tert-Butoxycarbonyl)-2-formyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine

To a solution of 6-(tert-butoxycarbonyl)-2-(trans- β -styryl)-4,5,6,7-tetrahydrooxazol[5,4-c]pyridine (803 mg) in tetrahydrofuran (16 ml) were added acetone (8.0 ml), water (4.0 ml), N-methylmorpholine oxide (577 mg) and osmium

tetraoxide (a 0.039 mole aqueous solution, 3.20 ml) at room temperature, followed by stirring overnight. Ethyl acetate (50 ml) and a 10% aqueous solution (50 ml) of sodium thiosulfate were added to the reaction mixture to separate it into layers. The water layer was extracted with ethyl acetate (30 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. A solution of the resulting residue in tetrahydrofuran (16 ml) were added methanol (8.0 ml), water (8.0 ml) and sodium metaperiodate (790 mg) at room temperature. After stirring for 3 hours, ethyl acetate (30 ml) and water (50 ml) were added to the reaction mixture to separate it into layers. The water layer was extracted with ethyl acetate (20 ml). The organic layers were combined, washed with a saturated aqueous solution of sodium bicarbonate (50 ml), dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 4:1 → 2:1), whereby the title compound (234 mg) was obtained as a colorless transparent glassy substance. $^1\text{H-NMR}$ (CDCl_3) δ : 1.49(9H,s), 2.77(2H,br s), 3.77(2H,br s), 4.62(2H,s), 9.70(1H,s).

The resulting aldehyde was unstable so that it was provided for the subsequent reaction immediately.

[Referential Example 425] 6-(tert-Butoxycarbonyl)-2-methoxycarbonyl-4,5,6,7-tetrahydrooxazol[5,4-c]pyridine

To a solution of 6-(tert-butoxycarbonyl)-2-formyl-4,5,6,7-tetrahydrooxazol[5,4-c]pyridine (225 mg) in methanol (9.0 ml) were added sodium cyanide (220 mg) and manganese dioxide (780 mg) at room temperature, followed by stirring for 30 minutes. The reaction mixture was subjected to Celite filtration by using ethyl acetate. The filtrate was washed with water (50 ml) and saturated saline (50 ml), dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:2 → 1:1), whereby the title compound (120 mg) was obtained as a colorless transparent glassy substance.

¹H-NMR (CDCl₃) δ: 1.49(9H,s), 2.73(2H,br s), 3.74(2H,br s), 4.01(3H,s), 4.59(2H,s).

MS (FAB) m/z: 283 (M+H)⁺.

[Referential Example 426] Lithium 6-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrooxazol[5,4-c]pyridine-2-carboxylate

To a solution of 6-(tert-butoxycarbonyl)-2-methoxycarbonyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine (311 mg) in tetrahydrofuran (8.0 ml) were added water (2.0 ml) and lithium hydroxide (25.0 mg) at room temperature. After stirring for 10 minutes, the reaction mixture was distilled under reduced pressure to remove the solvent,

whereby the title compound (280 mg) was obtained as a colorless solid. The residue was provided for the subsequent reaction without purification.

^1H -NMR (DMSO- d_6) δ : 1.42(9H,s), 3.31(2H,s),
5 3.60(2H,d,J=5.4Hz), 4.42(2H,s).

[Referential Example 427] 2-Methoxycarbonyl-6-methyl-
4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine

To a solution of 6-(tert-butoxycarbonyl)-2-
methoxycarbonyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine
10 (500 mg) in methylene chloride (15 ml) was added
trifluoroacetic acid (15 ml) at room temperature, followed
by stirring for 10 minutes. The reaction mixture was
concentrated under reduced pressure. To the resulting
residue were added methylene chloride (20 ml),
15 triethylamine (495 μl), acetic acid (205 μl), formalin (230
 μl) and sodium triacetoxyborohydride (570 mg) at room
temperature. After stirring for 15 minutes, methylene
chloride (20 ml) and a saturated aqueous solution (50 ml)
of sodium bicarbonate were added to the reaction mixture to
20 separate it into layers. The water layer was extracted
with methylene chloride (3 x 20 ml). The organic layers
were combined, dried over anhydrous sodium sulfate and
distilled under reduced pressure to remove the solvent.
The residue was purified by chromatography on a silica gel
25 column (chloroform : methanol = 20:1 \rightarrow 10:1), whereby the

title compound (257 mg) was obtained as a colorless transparent oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.52(3H,s), 2.72-2.78(2H,m), 2.78-2.83(2H,m), 3.61(2H,t,J=1.7Hz), 4.00(3H,s).

5 MS (FAB) m/z : 197 ($\text{M}+\text{H}$) $^+$.

[Referential Example 428] 1-(tert-Butoxycarbonyl)-4-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

To a solution of 2-methoxycarbonyl-6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine (250 mg) in
10 tetrahydrofuran (8.0 ml) were added water (2.0 ml) and lithium hydroxide (30.0 mg) at room temperature. After stirring for 10 minutes, the solvent was distilled off under reduced pressure. To a solution of the resulting
15 residue in N,N-dimethylformamide (4.0 ml) were added 1-(tert-butoxycarbonyl)piperazine (260 mg), 1-hydroxybenzotriazole monohydrate (189 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (268 mg) at room temperature. After stirring for 63 hours,
20 methylene chloride (20 ml) and a saturated aqueous solution (30 ml) of sodium bicarbonate were added to the reaction mixture to separate it into layers. The water layer was extracted with methylene chloride (2 x 10 ml). The organic layers were combined and washed with water (150 ml). The
25 resulting water layer was extracted with methylene chloride (3 x 10 ml). The organic layers were combined, dried over

anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 1:1 → 1:3), whereby the title compound (359 mg) was obtained as a colorless transparent viscous substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.48(9H,s), 2.51(3H,s), 2.71(2H,t,J=4.5Hz), 2.79(2H,t,J=4.5Hz), 3.51(4H,t,J=5.0Hz), 3.60(2H,s), 3.75(2H,t,J=5.0Hz), 4.22(2H,t,J=5.0Hz).

MS (FAB) m/z : 351 ($\text{M}+\text{H}$) $^+$.

[Referential Example 429] 6-(tert-Butoxycarbonyl)-2-methylthio-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine

To a solution of 1-(tert-butoxycarbonyl)-4-piperidone (9.30 g) in tetrahydrofuran (40 ml) was added N,N-dimethylformamide dimethylacetal (18.6 ml) at room

temperature, followed by heating under reflux for 3 days.

After the reaction mixture was allowed to cool down to room temperature, it was concentrated under reduced pressure.

To a solution of the resulting residue in ethanol (120 ml) were added methylisothiourea sulfate (19.5 g) and sodium

ethoxide (13.2 g) at room temperature, followed by heating under reflux for 5 hours. After the reaction mixture was

allowed to cool down, water (700 ml) and ethyl acetate (200 ml) were added to the reaction mixture to separate it into

layers. The water layer was then extracted with ethyl

acetate (200 ml). The organic layers were combined, washed with saturated saline (200 ml), dried over anhydrous sodium

sulfate and concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 20:1 → 15:1), whereby the title compound (1.82 g) was obtained as a colorless transparent viscous substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.49(9H,s), 2.56(3H,s), 2.89(2H,t,J=5.9Hz), 3.72(2H,t,J=5.9Hz), 4.52(2H,s), 8.27(1H,s).

MS (FAB) m/z : 282 ($\text{M}+\text{H}$) $^+$.

[Referential Example 430] 6-(tert-Butoxycarbonyl)-2-methylsulfonyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine

To a solution of 6-(tert-butoxycarbonyl)-2-methylthio-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (2.20 g) in methylene chloride (80 ml) was added metachloroperbenzoic acid (3.37 g). After stirring for 4 hours, a 10% aqueous solution (100 ml) of sodium thiosulfate and a saturated aqueous solution (100 ml) of sodium bicarbonate were added to the reaction mixture and the mixture was separated into layers. The water layer was extracted with methylene chloride (2 x 50 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 20:1 → 10:1), whereby the title compound (2.34 g) was obtained as a colorless solid.

¹H-NMR (CDCl₃) δ: 1.50 (9H, s), 3.10 (2H, t, J=5.9Hz),
3.34 (3H, s), 3.80 (2H, t, J=5.9Hz), 4.71 (2H, s), 8.63 (1H, s).

MS (FAB) m/z: 314 (M+H)⁺.

[Referential Example 431] 6-(tert-Butoxycarbonyl)-2-cyano-
5,6,7,8-tetrahydrocyano[4,3-d]pyrimidine

To a solution of 6-(tert-butoxycarbonyl)-2-methylsulfonyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (330 mg) in methylene chloride (10 ml) was added tetrabutylammonium cyanide (425 mg) at room temperature. After stirring at room temperature for 3 hours, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 20:1), whereby the title compound (261 mg) was obtained as pale yellow foam.

¹H-NMR (CDCl₃) δ: 1.50 (9H, s), 3.02 (2H, t, J=5.9Hz),
3.78 (2H, t, J=5.9Hz), 4.68 (2H, s), 8.55 (1H, s).

MS (FAB) m/z: 261 (M+H)⁺.

[Referential Example 432] 6-(tert-Butoxycarbonyl)-2-methoxycarbonyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine

To a solution of 6-(tert-butoxycarbonyl)-2-cyano-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (814 mg) in methanol (10 ml) was added concentrated sulfuric acid (5.0 ml) at room temperature. The resulting mixture was stirred at 100°C for 1 hour. After the reaction mixture was allowed to cool down, it was concentrated under reduced

pressure. The residue was dissolved in methylene chloride (15 ml), followed by the addition of triethylamine (2.20 ml) and di-tert-butyl dicarbonate (1.03 g) at room temperature. The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was then concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 6:1 → 3:1), whereby the title compound (619 mg) was obtained as a pale yellow viscous substance.

¹H-NMR (CDCl₃) δ: 1.50 (9H, s), 3.10 (2H, t, J=5.8 Hz), 3.79 (2H, t, J=5.8 Hz), 4.06 (3H, s), 4.71 (2H, s), 8.65 (1H, s).
MS (FAB) m/z: 294 (M+H)⁺.

[Referential Example 433] Lithium 6-methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridine-2-carboxylate

In the same manner as in Referential Example 371, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.30-2.60 (4H, m), 2.35 (3H, s), 3.34 (2H, s), 6.50 (1H, s).

[Referential Example 434] 1-(tert-Butoxycarbonyl)-4-[(6-methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.48(9H,s), 2.49(3H,s), 2.55-2.65(2H,m),
2.65-2.75(2H,m), 3.45-3.55(6H,m), 3.76(4H,br s),
6.86(1H,s).

MS (FAB) m/z : 350 ($\text{M}+\text{H}$) $^+$.

5 [Referential Example 435] Methyl 2-tert-
butoxycarbonylisoindoline-5-carboxylate

In the same manner as in Referential Example 363, the
title compound was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.52(9H,s), 3.92(3H,s), 4.65-4.72(2H,m),
10 4.73(2H,s), 7.29(0.5H,d,J=7.8Hz), 7.34(0.5H,d,J=7.8Hz),
7.91(0.5H,s), 7.96(1H,s), 7.98(0.5H,s).

MS (FAB) m/z : 278 ($\text{M}+\text{H}$) $^+$.

Elementary analysis for $\text{C}_{15}\text{H}_{19}\text{NO}_4$

Calculated: C, 64.97; H, 6.91; N, 5.05.

15 Found: C, 64.94; H, 7.13; N, 4.96.

In the same manner as in Referential Example 368,
compounds shown in Referential Examples 436 and 437 were
obtained.

[Referential Example 436] 2-tert-
20 Butoxycarbonylisoindoline-5-carboxylic acid

$^1\text{H-NMR}$ (CDCl_3) δ : 1.53(9H,s), 4.70-4.72(2H,m), 4.75(2H,s),
7.32(0.5H,d,J=7.3Hz), 7.38(0.5H,d,J=7.3Hz), 7.97(0.5H,s),
8.02(1H,s), 8.04(0.5H,s).

MS (FAB) m/z : 264 ($\text{M}+\text{H}$) $^+$.

25 Elementary analysis for $\text{C}_{14}\text{H}_{17}\text{NO}_4$

Calculated: C, 63.87; H, 6.51; N, 5.32.

Found: C, 63.79; H, 6.65; N, 5.12.

[Referential Example 437] 4-tert-Butoxycarbonyl-3-carboxymethyl-1-[(5-chloroindol-2-yl)sulfonyl]piperazine

5 ^1H -NMR (DMSO- d_6) δ : 1.33(9H,s), 2.12-2.25(1H,m), 2.30-2.42(2H,m), 2.35-3.57(1H,m), 2.60-2.71(1H,m), 2.90-3.02(1H,m), 3.54-3.65(1H,m), 3.72-3.86(2H,m), 4.43(1H,br s), 6.99(1H,s), 7.30(1H,dd,J=8.8,1.8Hz), 7.48(1H,d,J=8.8Hz), 7.75(1H,d,J=1.8Hz).

10 MS (FAB) m/z : 480 (M+Na) $^+$.

[Referential Example 438] 4-tert-Butoxycarbonyl-1-[(5-chloroindol-2-yl)sulfonyl]-3-[N-(2-hydroxyethyl)carbamoylmethyl]piperazine

In the same manner as in Referential Example 5, the
15 title compound was obtained.

^1H -NMR (CDCl $_3$) δ : 1.40(9H,s), 2.30-2.90(3H,m), 3.03-4.15(7H,m), 4.62-4.71(1H,m), 6.56(1H,br s), 6.95(1H,s), 7.28(1H,dd,J=8.8,1.7Hz), 7.37(1H,d,J=8.8Hz), 7.64(1H,d,J=1.7Hz), 10.01-10.70(1H,br m).

20 FAB-MS m/z : 502 [(M+H) $^+$, Cl 35], 504 [(M+H) $^+$, Cl 37].

[Referential Example 439] 4-[(5-Chloro-1-phenylsulfonyl-indol-2-yl)sulfonyl]-1-(tert-butoxycarbonyl)-2-(2-hydroxyethyl)piperazine

In tetrahydrofuran - methanol (10/1, 55 mL) was
25 dissolved 4-(tert-butoxycarbonyl)-1-[(5-chloro-1-

phenylsulfonylindol-2-yl)sulfonyl]-3-

[(methoxycarbonyl)methyl]piperazine (2.5 g), followed by the addition of lithium borohydride (135 mg). The resulting mixture was stirred for 48 hours. The solvent was distilled off under reduced pressure. Water and chloroform were then added to the reaction mixture and the mixture was separated into layers. The organic layer was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to chromatography on a silica gel column (ethyl acetate : hexane = 2:3), whereby the title compound (1.84 g) was obtained as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.47(9H,s), 1.60(2H,m), 2.98-4.42(9H,m), 7.42-7.59(6H,m), 8.01(1H,d,J=1.2Hz), 8.03(1H,d,J=1.2Hz), 8.21(1H,d,J=9.3Hz).

MS (FAB) m/z : 584 $[(\text{M}+\text{H})^+]$.

[Referential Example 440] 4-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-1-(tert-butoxycarbonyl)-2-(formylmethyl)piperazine

In the same manner as in Referential Example 285, the title compound was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.45(9H,s), 2.64(1H,dd,J=5.4,17.4Hz), 2.95-3.15(5H,m), 3.72(1H,d,J=13.2Hz), 3.94(1H,m), 4.73(1H,m), 7.40-7.58(6H,m), 8.00(1H,d,J=1.2Hz), 8.02(1H,d,J=1.2Hz), 8.20(1H,d,J=9.0Hz), 9.62(1H,s).

[Referential Example 441] 4-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-1-(tert-butoxycarbonyl)-2-[2-(1,4-dioxo-8-azaspiro[4,5]-decan-8-yl)ethyl]piperazine

In the same manner as in Referential Example 265, the title compound was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.45 (9H, s), 1.68 (4H, t, $J=6.4\text{Hz}$), 1.83-3.20 (12H, m), 3.61 (1H, m), 3.94 (4H, s), 4.0-4.25 (2H, m), 7.39-7.58 (6H, m), 8.01 (1H, d, $J=1.5\text{Hz}$), 8.04 (1H, d, $J=1.0\text{Hz}$), 8.22 (1H, d, $J=9.3\text{Hz}$).

MS (FAB) m/z : 709 $[(M+H)^+]$.

[Referential Example 442] 4-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-1-(tert-butoxycarbonyl)-2-[(1,3-dioxolan-2-yl)methyl]piperazine

In toluene (10 mL) were dissolved 4-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-1-(tert-butoxycarbonyl)-2-(formylmethyl)piperazine (440 mg) and ethylene glycol (71 mg), followed by the addition of $p\text{-TsOH} \cdot \text{H}_2\text{O}$ (15 mg). The resulting mixture was heated to 60°C and stirred for 16 hours. Ethyl acetate was added to the reaction mixture.

The resulting mixture was washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over anhydrous MgSO_4 and distilled under reduced pressure to remove the solvent, whereby the title compound (460 mg) was obtained as colorless amorphous.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.45 (9H, s), 1.63 (2H, m), 1.98 (2H, m), 2.49-3.95 (3H, m), 3.66-4.13 (8H, m), 4.78 (1H, t, $J=4.9\text{Hz}$), 7.17 (1H, m), 7.42-7.58 (5H, m), 8.02 (1H, d, $J=1.5\text{Hz}$), 8.04 (1H, d, $J=1.0\text{Hz}$), 8.23 (1H, d, $J=9.3\text{Hz}$).

5 MS (FAB) m/z : 626 $[(M+H)^+]$.

[Referential Example 443] 1,4-Dibenzyl-2-[(1,3-dioxoisindol-2-yl)methyl]piperazine

To a solution of 1,4-dibenzyl-2-(hydroxymethyl)piperazine (1.51 g), phthalimide (0.790 g)
10 and triphenylphosphine (1.40 g) in tetrahydrofuran (20 ml) was added a 40% toluene solution (2.34 ml) of diethyl azodicarboxylate under ice cooling. The resulting mixture was stirred at room temperature for 6 hours. Furthermore, 1,4-dibenzyl-2-(hydroxymethyl)piperazine (0.87 g),
15 phthalimide (0.486 g), triphenylphosphine (0.81 g) and tetrahydrofuran (5 ml) were added to the reaction mixture, followed by the addition of a 40% toluene solution (1.34 ml) of diethyl azodicarboxylate under ice cooling. The resulting mixture was stirred at room temperature for 18.5
20 hours. Phthalimide (0.405 g) and a 40% toluene solution (1.10 ml) of diethyl azodicarboxylate were added under ice cooling, followed by stirring at room temperature for 20 hours. The solvent was distilled off under reduced pressure. The residue was subjected to column
25 chromatography twice (3% methanol - methylene chloride for the first time and ethyl acetate / hexane = 1/3 for the

second time) using as a carrier silica gel, whereby a crude product was obtained. The crude product was crystallized from hexane - methylene chloride, collected by filtration and washed with hexane, whereby the title compound (0.243 g) was obtained as colorless powder.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.30-2.40 (4H,m), 2.50-2.60 (1H,m), 2.95-3.10 (2H,m), 3.40-3.55 (2H,m), 3.60-3.65 (1H,m), 3.75-3.80 (1H,m), 3.95-4.05 (1H,m), 4.15-4.25 (1H,m), 7.10-7.35 (10H,m), 7.70-7.75 (2H,m), 7.80-7.85 (2H,m).

MS (FAB) m/z : 426 ($\text{M}+\text{H}$) $^+$.

[Referential Example 444] 1-[(5-Chloro-1-phenylsulfonyl)piperazin-2-yl]-3-[(1,4-dioxoisoindol-2-yl)methyl]piperazine

In the same manner as in Referential Example 266, the title compound was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.77-2.88 (2H,m), 2.98-3.09 (2H,m), 3.16-3.18 (1H,m), 3.69-3.72 (3H,m), 3.81 (1H,broad d, $J=12.6\text{Hz}$), 7.36 (1H,s), 7.40-7.46 (3H,m), 7.52-7.56 (2H,m), 7.71-7.74 (2H,m), 7.83-7.86 (2H,m), 7.99 (2H,dd, $J=1.1, 7.4\text{Hz}$), 8.22 (1H,d, $J=9.2\text{Hz}$).

MS (FAB) m/z : 599 [$\text{M}+\text{H}$] $^+$, Cl^{35}], 601 [$\text{M}+\text{H}$] $^+$, Cl^{37}].

[Referential Example 445] 1,4-Di(tert-butoxycarbonyl)-2-(2-phenoxyethyl)piperazine

To a solution of 1,4-di(tert-butoxycarbonyl)-2-(2-hydroxyethyl)piperazine (0.660 g, 2 mmol) and

triphenylphosphine (0.577 g, 2.2 mmol) in tetrahydrofuran (10 ml) were added a solution of phenol (0.188 g, 2 mmol) in tetrahydrofuran (5 ml) and diethyl azodicarboxylate (0.35 ml, 2.2 mmol), followed by stirring at room temperature for 4 hours. The reaction mixture was purified by flash column chromatography (ethyl acetate / n-hexane = 1/4) using as a carrier silica gel, whereby the title compound (0.611 g, 75%) was obtained as a colorless solid.

¹H-NMR (CDCl₃) δ: 1.38(9H,s), 1.46(9H,s), 1.91-1.96(1H,m), 2.06-2.12(1H,m), 2.81-3.00(2H,broad), 3.94-3.98(6H,m), 4.40(1H,broad), 6.86(2H,d,J=7.8Hz), 6.92(1H,dd,J=7.2,7.2Hz), 7.23-7.27(2H,m).

MS (FAB) m/z: 407 (M+H)⁺.

[Referential Example 446] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-(2-phenoxyethyl)piperazine

In the same manner as in Referential Example 220, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.81-1.86(2H,m), 2.70-2.76(1H,m), 2.93-3.07(4H,m), 3.76-3.85(2H,m), 4.05(2H,t,J=5.8Hz), 6.84(2H,d,J=7.8Hz), 6.92-6.96(1H,m), 7.36(1H,s), 7.40-7.45(4H,m), 7.50-7.56(3H,m), 8.00(2H,d,J=7.5Hz), 8.22(1H,d,J=9.2Hz).

MS (FAB) m/z: 560 [(M+H)⁺, Cl³⁵], 562 [(M+H)⁺, Cl³⁷].

[Referential Example 447] 1,4-Di(tert-butoxycarbonyl)-2-[2-(2-naphthoxy)ethyl]piperazine

In the same manner as in Referential Example 445, the title compound was obtained.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.38(9H,s), 1.47(9H,s), 1.99-2.04(1H,m), 2.16(1H,m), 2.82-3.02(2H,broad), 4.00-4.12(6H,broad m), 4.46(1H,broad), 7.09-7.12(2H,m), 7.29-7.33(1H,m), 7.39-7.43(1H,m), 7.67-7.75(3H,m).
MS (FAB) m/z : 457 ($\text{M}+\text{H}$) $^+$.

10 [Referential Example 448] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-[2-(2-naphthoxy)ethyl]piperazine

In the same manner as in Referential Example 220, the title compound was obtained.

15 $^1\text{H-NMR}$ (CDCl_3) δ : 1.89-1.95(2H,m), 2.73-2.79(1H,m), 2.92-3.09(4H,m), 3.79(1H,broad d, $J=10.9\text{Hz}$), 3.87(1H,broad d, $J=12.2\text{Hz}$), 4.18(2H,t, $J=6.0\text{Hz}$), 7.06-7.10(2H,m), 7.31-7.35(1H,m), 7.36(1H,s), 7.39-7.48(5H,m), 7.52-7.56(1H,m), 7.69-7.72(2H,m), 7.76(1H,d, $J=8.3\text{Hz}$), 8.00(2H,d, $J=7.8\text{Hz}$),
20 8.22(1H,d, $J=9.2\text{Hz}$).

MS (FAB) m/z : 610 [$(\text{M}+\text{H})^+$, Cl^{35}], 612 [$(\text{M}+\text{H})^+$, Cl^{37}].

[Referential Example 449] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-[2-(tert-butyldiphenylsilyloxy)ethyl]piperazine

In the same manner as in Referential Example 266, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.01 (9H, s), 1.55-1.61 (2H, m), 2.63-2.68 (1H, m), 2.88-3.01 (4H, m), 3.73-3.80 (4H, m), 7.33-7.45 (10H, m), 7.49-7.56 (2H, m), 7.61-7.64 (4H, m), 8.01 (2H, dd, J=1.1, 8.4 Hz), 8.22 (1H, d, J=9.3 Hz).

MS (FAB) m/z: 722 (M+H)⁺.

[Referential Example 450] 1-(tert-Butoxycarbonyl)-2-[2-(tert-butyldiphenylsilyloxy)ethyl]-4-[(1-phenylsulfonyl-5-chloroindol-2-yl)sulfonyl]piperazine

In the same manner as in Example 363, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.00 (9H, s), 1.38 (9H, s), 1.84-1.92 (2H, m), 2.86-2.93 (1H, m), 3.02-3.14 (2H, m), 3.32 (1H, broad), 3.58-3.62 (2H, m), 3.92 (2H, broad d, J=12.4 Hz), 4.42 (1H, broad), 7.29 (1H, s), 7.32-7.43 (10H, m), 7.51-7.58 (5H, m), 7.99-8.01 (2H, m), 8.17 (1H, d, J=9.0 Hz).

MS (FAB) m/z: 822 (M+H)⁺.

[Referential Example 451] 1-(tert-Butoxycarbonyl)-4-[(5-chloroindol-2-yl)sulfonyl]-2-(2-hydroxyethyl)piperazine

To a solution of 4-[(1-benzenesulfonyl-5-chloroindol-2-yl)sulfonyl]-1-(tert-butoxycarbonyl)-2-[2-(tert-butyldiphenylsilyloxy)ethyl]piperazine (4.48 g) in tetrahydrofuran (20 ml) was added a 1.0M tetrahydrofuran solution (5.5 ml) of tetrabutylammonium fluoride, followed

by stirring at room temperature for 3.5 hours. After concentration under reduced pressure, the residue was purified by flash column chromatography (ethyl acetate : hexane = 1:9 to 1:0) using as a carrier silica gel, whereby the title compound (0.75 g) was obtained as a colorless solid.

^1H -NMR (DMSO- d_6) δ : 1.33(9H,s), 1.74-1.77(2H,m), 2.24-2.40(2H,m), 3.04(1H,m), 3.35-3.46(2H,m), 3.56-3.63(2H,m), 3.85-3.88(1H,broad d, $J=13.2\text{Hz}$), 4.25(1H,broad), 4.43(1H,broad), 6.98(1H,d, $J=0.7\text{Hz}$), 7.29(1H,dd, $J=1.9, 8.8\text{Hz}$), 7.46-7.48(1H,m), 7.74(1H,m).

MS (FAB) m/z : 444 ($M+H$) $^+$.

[Referential Example 452] 1,4-Bis(tert-butoxycarbonyl)-2-(2-tosyloxyethyl)piperazine

A solution of 1,4-di(tert-butoxycarbonyl)-2-(2-hydroxyethyl)piperazine (5.05 g) and p-toluenesulfonyl chloride (4.34 g) in methylene chloride (200 ml) was cooled to 0°C, followed by the dropwise addition of triethylamine (11 ml). The resulting mixture was stirred at 0°C for 1 hour and at room temperature for 1 day. The reaction mixture was concentrated under reduced pressure. After dilution with ethyl acetate, the residue was washed with 1N hydrochloric acid, water and saturated aqueous NaCl solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate /

hexane = 1/4 to 1/1) using, as a carrier, silica gel, whereby the title compound (4.82 g) was obtained as a colorless solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.44 (18H, s), 1.78-1.84 (1H, m),
5 1.94 (1H, broad), 2.44 (3H, s), 2.86 (3H, broad), 3.85 (2H, broad),
3.97-4.07 (3H, m), 4.21 (1H, broad), 7.33 (2H, d, $J=8.3\text{Hz}$),
7.77 (2H, d, $J=8.3\text{Hz}$).

MS (FAB) m/z : 485 ($\text{M}+\text{H}$) $^+$.

[Referential Example 453] 1,4-Bis(tert-butoxycarbonyl)-2-
10 [2-(2-oxo-1,3-oxazolan-3-yl)ethyl]piperazine

To a suspension of sodium hydride (60%, 57 mg) in N,N-dimethylformamide (20 ml), 2-oxazolidone (0.122 g) was added, followed by stirring at 90°C for 1 hour. A solution of 1,4-di(tert-butoxycarbonyl)-2-(2-
15 tosyloxyethyl)piperazine (0.686 g) in N,N-dimethylformamide (15 ml) was added to the reaction mixture. The resulting mixture was stirred at 90°C for 4 hours. The reaction mixture was concentrated under reduced pressure. The residue was diluted with ethyl acetate, washed with water
20 and saturated aqueous NaCl solution, dried over magnesium sulfate and concentrated under reduced pressure, whereby the title compound (0.515 g) was obtained as a colorless solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.46 (8H, s), 1.47 (10H, s), 1.78-1.85 (2H, m),
25 2.81-2.95 (3H, m), 3.39-3.64 (2H, m), 3.85-4.05 (2H, broad),

4.00 (2H, broad d, $J=13.4\text{ Hz}$), 4.09-4.28 (2H, m), 4.30-4.34 (2H, m).

MS (FAB) m/z : 400 ($M+H$)⁺.

[Referential Example 454] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-[2-(2-oxo-1,3-oxazolan-3-yl)ethyl]piperazine

In the same manner as in Referential Example 220, the title compound was obtained.

¹H-NMR (CDCl₃) δ : 1.51-1.76 (2H, m), 2.69-2.74 (1H, m), 2.77-2.85 (2H, m), 2.96-3.03 (2H, m), 3.20-3.27 (1H, m), 3.48-3.55 (2H, m), 3.59-3.69 (2H, m), 3.83 (1H, broad d, $J=11.7\text{ Hz}$), 4.30-4.40 (2H, m), 7.39-7.46 (4H, m), 7.51-7.57 (2H, m), 7.99-8.02 (2H, m), 8.22 (1H, d, $J=9.0\text{ Hz}$).

MS (FAB) m/z : 553 [$(M+H)^+$, Cl³⁵], 555 [$(M+H)^+$, Cl³⁷].

[Referential Example 455] 4,5-Bis(bromomethyl)thiazole

At room temperature, 4,5-dimethylthiazole (5.00 g), N-bromosuccinic imide (15.7 g) and α,α' -azobisisobutyronitrile (362 mg) were dissolved in ethylene dichloride (500 ml), followed by heating under reflux for 1 hour. After completion of the reaction, the solvent was distilled off and the residue was purified by chromatography on a silica gel column (hexane : diethyl ether = 1:4), whereby the title compound (5.24 g, 44%) was obtained.

¹H-NMR (CDCl₃) δ : 4.64 (2H, s), 4.74 (2H, s), 8.75 (1H, s).

[Referential Example 456] 5,6-Dimethyl-4,5,6,7-tetrahydrothiazolo[4,5-d]pyridazine

Under ice cooling, 4,5-bis(bromomethyl)thiazole (600 mg) and 1,2-dimethylhydrazine dihydrochloride (294 mg) were suspended in ethanol (20 ml). Triethylamine (1.23 ml) was added in one portion to the reaction mixture, followed by stirring at room temperature for 30 minutes and then, at 50°C for 30 minutes. The solvent was distilled off and the residue was purified by chromatography on a silica gel column (5% methanol - methylene chloride), whereby the title compound (90 mg, 24%) was obtained.

¹H-NMR (CDCl₃) δ: 2.43(3H,s), 2.56(3H,s), 3.92(2H,s), 4.06(2H,br s), 8.68(1H,s).

MS (FAB) m/z: 170 (M+H)⁺.

[Referential Example 457] 3-(Methoxycarbonylmethyl)-1-[[1-phenylsulfonyl-5-(trimethylsilylethynyl)indol-2-yl]sulfonyl]piperazine

In the same manner as in Referential Example 226, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 0.25(9H,s), 2.38(1H,dd,J=16.2,8.8Hz), 2.46(1H,dd,J=16.2,4.2Hz), 2.76(1H,dd,J=12.5,10.0Hz), 2.91-2.99(1H,m), 2.99-3.07(2H,m), 3.17-3.25(1H,m), 3.67(3H,s), 3.69-3.78(2H,m), 7.38-7.44(3H,m), 7.54(1H,t,J=7.6Hz), 7.58(1H,dd,J=8.9,1.6Hz), 7.68(1H,d,J=1.6Hz), 7.98-8.02(2H,m), 8.22(1H,d,J=8.9Hz).

MS (FAB) m/z: 574 (M+H)⁺.

[Referential Example 458] 1,4-Bis(t-butoxycarbonyl)-2-[2-[(morpholin-4-yl)sulfonyl]ethyl]piperazine

In the same manner as in Referential Example 293, the
5 title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.47(18H,s), 1.95-2.00(1H,m), 2.10-2.20(1H,m), 2.70-3.10(5H,m), 3.25(4H,t,J=4.7Hz), 3.75(4H,t,J=4.7Hz), 3.80-4.30(4H,m).

MS (FAB) m/z: 464 (M+H)⁺.

10 [Referential Example 459] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-[2-[(morpholin-4-yl)sulfonyl]ethyl]piperazine

In the same manner as in Referential Example 220, the
title compound was obtained.

15 ¹H-NMR (CDCl₃) δ: 1.80-1.90(1H,m), 1.90-2.00(1H,m), 2.60-2.70(1H,m), 2.80-3.10(6H,m), 3.20-3.30(4H,m), 3.60-3.85(6H,m), 7.40-7.50(4H,m), 7.50-7.60(2H,m), 8.00-8.10(2H,m), 8.22(1H,d,J=9.1Hz).

MS (FAB) m/z: 617 [(M+H)⁺, Cl³⁵], 619 [(M+H)⁺, Cl³⁷].

20 [Referential Example 460]

1,4-Bis(tert-butoxycarbonyl)-2-hydroxymethylpiperazine

In the same manner as in Referential Example 284, the
title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.46-1.47(18H,m), 2.70-4.400(10H).

[Referential Example 461] 1,4-Bis(tert-butoxycarbonyl)-2-formylpiperazine

In the same manner as in Referential Example 285, the title compound was obtained.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.45-1.50 (18H,m), 2.80-3.00 (1H,m), 3.00-3.20 (2H,m), 3.70-4.00 (2H,m), 4.40-4.70 (2H,m), 9.59 (1H,s).
MS (FAB) m/z : 315 ($\text{M}+\text{H}$) $^+$.

[Referential Example 462] 1,4-Bis(tert-butoxycarbonyl)-2-(2-ethoxycarbonylethenyl)piperazine

10 In a 50-ml two-necked flask, sodium hydride (141 mg, 60% in oil) was charged, followed by purging with argon. Tetrahydrofuran (5 ml) was added and then, triethyl phosphonoacetate (700 μl) was added under ice cooling. The resulting mixture was stirred at room temperature for 15
15 minutes. The reaction mixture was cooled again and under ice cooling, a solution of 1,4-bis(tert-butoxycarbonyl)-2-formylpiperazine (911 mg) dissolved in tetrahydrofuran (7 ml) was added dropwise, followed by stirring at room temperature for 4 hours. After completion of the reaction,
20 water was added and then ethyl acetate was added, whereby the mixture was separated into layers. The organic layer thus obtained was washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue
25 was subjected to flash column chromatography (hexane : ethyl acetate = 2:1) using, as a carrier, silica gel,

whereby the title compound (920 mg, 83%) was obtained as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.20-1.30 (3H,m), 1.40-1.50 (18H,m), 2.75-3.20 (3H,m), 3.80-4.80 (6H,m), 5.93 (1H,dd, $J=15.9, 2.0\text{Hz}$),
5 6.82 (1H,dd, $J=15.9, 4.4\text{Hz}$).

MS (FAB) m/z : 385 ($\text{M}+\text{H}$) $^+$.

[Referential Example 463] 1,4-Bis(tert-butoxycarbonyl)-2-(2-ethoxycarbonylethyl)piperazine

10 In the same manner as in Referential Example 287, the title compound was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.25 (3H,t, $J=7.1\text{Hz}$), 1.46 (9H,s), 1.46 (9H,s), 1.70-1.85 (1H,m), 1.85-2.00 (1H,m), 2.20-2.40 (2H,m), 2.70-3.00 (3H,m), 3.80-4.20 (6H,m).

MS (FAB) m/z : 387 ($\text{M}+\text{H}$) $^+$.

15 [Referential Example 464] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-(2-ethoxycarbonylethyl)piperazine

In the same manner as in Referential Example 220, the title compound was obtained.

20 $^1\text{H-NMR}$ (CDCl_3) δ : 1.25 (3H,t, $J=7.2\text{Hz}$), 1.30-1.80 (3H,m), 2.30-2.45 (2H,m), 2.55-2.65 (1H,m), 2.75-3.05 (4H,m), 3.70-3.80 (2H,m), 4.11 (2H,q, $J=7.2\text{Hz}$), 7.35-7.50 (4H,m), 7.50-7.60 (2H,m), 8.02 (2H,d, $J=7.3\text{Hz}$), 8.22 (1H,d, $J=9.3\text{Hz}$).

MS (FAB) m/z : 540 [$(\text{M}+\text{H})^+$, Cl^{35}], 542 [$(\text{M}+\text{H})^+$, Cl^{37}].

[Referential Example 465] 1,4-Bis(tert-butoxycarbonyl)-2-(2-cyanoethyl)piperazine

To an aqueous solution (3.0 ml) of potassium cyanide (85.0 mg) was added a solution of 1,4-bis(t-
5 butoxycarbonyl)-2-(2-bromoethyl)piperazine (393 mg) in ethanol (3.0 ml), followed by stirring under heat at 110°C for 3 hours. After the removal of ethanol by distillation under reduced pressure, methylene chloride (100 ml) was added to the residue. The organic layer was washed with
10 distilled water until the water phase became neutral. The resulting organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (silica
15 gel 15 g, hexane : ethyl acetate = 2:1), whereby the title compound (145.0 mg, 43%) was obtained as a white solid.

¹H-NMR (CDCl₃) δ: 1.47(12H,s), 1.49(6H,s), 1.75-1.88(1H,m), 1.92-2.10(1H,m), 2.28-2.35(2H,m), 2.70-3.10(3H,m), 3.80-4.15(3H,m), 4.20-4.30(1H,m).

20 MS (FAB) m/z: 340 (M+H)⁺.

[Referential Example 466] 4-[(1-Phenylsulfonyl-5-chloroindol-2-yl)sulfonyl]-2-(2-cyanoethyl)piperazine

In the same manner as in Referential Example 220, the title compound was obtained.

25 ¹H-NMR (DMSO-d₆) δ: 1.65-1.77(1H,m), 1.78-1.90(1H,m), 2.48(2H,t,J=7.6Hz), 2.70(1H,dd,J=12.5,9.5Hz), 2.85-

3.10 (4H,m), 3.62-3.70 (1H,m), 3.75-3.85 (1H,m), 7.40-
7.50 (4H,m), 7.55-7.60 (2H,m), 8.01 (2H,dd,J=8.6,1.2Hz),
8.22 (1H,d,J=9.0Hz).

MS (FAB) m/z: 493 [(M+H)⁺, Cl³⁵], 495 [(M+H)⁺, Cl³⁷].

5 [Referential Example 467] 2-Amino-6,6-ethylenedioxy-
4,5,6,7-tetrahydrobenzo[d]thiazole

In a 200-ml egg-plant type flask, 1,4-cyclohexanedione
ethylene ketal (7.80 g) was charged and dissolved in
cyclohexane (20 mL). To the resulting solution were added
10 pyrrolidine (4.35 mL) and p-toluenesulfonic acid
monohydrate (48.0 g), followed by heating under reflux
while water was trapped by a Dean and Stark apparatus.
After 70 minutes, the reaction mixture was cooled to room
temperature and the solvent was decanted and concentrated
15 under reduced pressure. The residue was dissolved in
methanol (15 ml). While attention was paid so as not to
occur a temperature rise due to water bath, sulfur powder
(1.60 g) was added to the resulting solution. After 15
minutes, a solution of cyanamide (2.10 g) in methanol (10
20 mL) was added dropwise over 20 minutes. After 14 hours,
the solvent was distilled off under reduced pressure. The
residue was subjected to chromatography on a silica gel
column (silica gel: 300 g, methylene chloride : methanol =
100:5 → 10:1), whereby the title compound (8.89 g) was
25 obtained as a dark green solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.96 (2H, t, $J=6.4\text{Hz}$), 2.74 (2H, t, $J=6.4\text{Hz}$),
2.81 (2H, s), 4.02 (4H, s), 4.77 (2H, br s).

MS (FAB) m/z : 213 ($\text{M}+\text{H}$) $^+$.

[Referential Example 468] 2-Chloro-6,6-ethylenedioxy-

5 4,5,6,7-tetrahydrobenzo[d]thiazole

Copper (II) chloride (760 mg) was charged in a 100-mL egg-plant type flask and dissolved in acetonitrile (10 mL). While cooling over water bath, tert-butyl nitrite (730 mg) was added in one portion to the resulting solution. After
10 10 minutes, 2-amino-6,6-ethylenedioxy-4,5,6,7-tetrahydrobenzo[d]thiazole (1.00 g) was added over about 50 minutes, followed by stirring at room temperature for 1 hour. The reaction mixture was then heated to 65°C and stirring was continued for 2 hours. After silica gel (5 g)
15 was added to the reaction mixture, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (silica gel: 50 g, hexane : ethyl acetate = 3:1), whereby the title compound (860 mg) was obtained as a yellow oil.

20 $^1\text{H-NMR}$ (CDCl_3) δ : 2.00 (2H, t, $J=6.4\text{Hz}$), 2.91 (4H, m),
4.03 (4H, s).

MS (FAB) m/z : 232 [$(\text{M}+\text{H})^+$, Cl^{35}], 234 [$(\text{M}+\text{H})^+$, Cl^{37}].

[Referential Example 469] 6,6-Ethylenedioxy-4,5,6,7-tetrahydrobenzo[d]thiazole

In a 100-mL egg-plant type flask, 2-chloro-6,6-ethylenedioxy-4,5,6,7-tetrahydrobenzo[d]thiazole (860 mg) was charged and was dissolved in methanol (10 mL). To the resulting solution were added 10% palladium-carbon (100 mg) and sodium acetate (305 mg), followed by stirring under a hydrogen gas stream of 4.5 atmospheric pressure. After 17 hours, palladium was filtered off and the solvent was distilled off under reduced pressure. The residue was subjected to chromatography on a silica gel column (silica gel: 50 g, ethyl acetate : hexane = 1:1), whereby the title compound (720 mg) was obtained as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.04 (2H, t, $J=6.8\text{Hz}$), 3.03 (4H, m), 4.05 (4H, s), 8.62 (1H, s).

MS (FAB) m/z : 198 ($\text{M}+\text{H}$) $^+$.

[Referential Example 470] Lithium (6,6-ethylenedioxy-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)carboxylate

In the same manner as in Referential Example 371, the title compound was obtained.

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 1.94 (2H, t, $J=6.6\text{Hz}$), 3.34-3.44 (4H, m), 3.95 (4H, s).

[Referential Example 471] 2-Amino-4,5-dihydro-7H-pyrano[4,3-d]thiazole

In the same manner as in Referential Example 467, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.66-2.70 (2H,m), 3.97 (2H,t,J=5.6Hz),
4.63 (2H,s), 4.94 (2H,br s).

MS (FAB) m/z: 157 (M+H)⁺.

[Referential Example 472] 2-Chloro-4,5-dihydro-7H-
5 pyrano[4,3-d]thiazole

In the same manner as in Referential Example 468, the
title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.85-2.89 (2H,m), 4.02 (2H,t,J=5.6Hz),
4.73 (2H,s).

10 MS (FAB) m/z: 175 [(M+H)⁺, Cl³⁵], 177 [(M+H)⁺, Cl³⁷].

[Referential Example 473] 4,5-Dihydro-7H-pyrano[4,3-
d]thiazole

In the same manner as in Referential Example 469, the
title compound was obtained.

15 ¹H-NMR (CDCl₃) δ: 2.97-3.01 (2H,m), 4.04 (2H,t,J=5.6Hz),
4.87 (2H,s), 8.69 (1H,s).

MS (FAB) m/z: 142 (M+H)⁺.

[Referential Example 474] Lithium (4,5-dihydro-7H-
pyrano[4,3-d]thiazol-2-yl)carboxylate

20 In a 200-mL three-necked flask, 4,5-dihydro-7H-
pyrano[4,3-d]thiazole (1.14 g) was added and dissolved in
ether (30 mL). After cooling to -78°C, 1.6M butyl lithium
(6.6 mL) was added and the resulting mixture was stirred.
After 20 minutes, a carbon dioxide gas was introduced.

25 After about 15 minutes, the introduction was terminated.

The reaction mixture was allowed to rise back to room temperature and concentrated under reduced pressure, whereby the title compound (1.65 g) was obtained as a colorless amorphous substance.

5 ^1H -NMR (DMSO- d_6) δ : 2.83 (2H, t, $J=5.6\text{Hz}$), 3.92 (2H, t, $J=5.6\text{Hz}$), 4.73 (2H, s).

[Referential Example 475] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[N-(phenylsulfonyl)carbamoyl]methyl]piperazine
10 trifluoroacetate

In tetrahydrofuran (10 ml) was dissolved 1-tert-butoxycarbonyl-2-carboxymethyl-4-[(5-chloroindol-2-yl)sulfonyl]piperazine (1.00 g), followed by the addition of carbonyldiimidazole (1.06 g). The resulting mixture was
15 heated overnight under reflux. After cooling to room temperature, the reaction mixture was added with benzenesulfonamide (685 mg), 1,8-diazabicyclo[5.4.0]-7-undecene (0.64 ml) and carbonyldiimidazole (353 mg). The resulting mixture was heated under reflux for 1 hour. The
20 reaction mixture was then concentrated under reduced pressure. Dichloromethane was added to the residue and the solid thus precipitated was filtered off. The filtrate was washed successively with 1N hydrochloric acid and saturated aqueous NaCl solution. The organic layer was dried over
25 anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified

by chromatography on a silica gel column (Φ 3.0 x 10.0 cm, dichloromethane : methanol = 100:1), whereby pale brown foam was obtained. The resulting foam was dissolved in dichloromethane (10 ml), followed by the addition of
 5 trifluoroacetic acid (10 ml). After stirring at room temperature for 1 minute, the reaction mixture was concentrated under reduced pressure. Diethyl ether was added to the residue and the resulting precipitate was collected by filtration, whereby the title compound (496
 10 mg, 31%) was obtained as colorless foam.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.60-2.75(3H,m), 3.10-3.20(1H,m), 3.29-3.38(1H,m), 3.53-3.73(4H,m), 7.06(1H,d,J=2.0Hz), 7.34(1H,dd,J=8.8,2.0Hz), 7.50(1H,d,J=8.8Hz), 7.64(2H,t,J=7.1Hz), 7.74(1H,t,J=7.1Hz), 7.80(1H,d,J=2.0Hz),
 15 7.93(2H,d,J=7.1Hz), 12.53(1H,s).

MS (FAB) m/z : 497 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 499 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Referential Example 476] 1-tert-Butoxycarbonyl-4-[(5-chloroindol-2-yl)sulfonyl]-2-[(N-methylsulfonylcarbonyl)methyl]piperazine

20 In tetrahydrofuran (10 ml) was dissolved 1-tert-butoxycarbonyl-2-carboxymethyl-4-[(5-chloroindol-2-yl)sulfonyl]piperazine (1.00 g), followed by the addition of carbonyldiimidazole (1.06 g). The resulting mixture was heated overnight under reflux. After cooling to room
 25 temperature, methanesulfonamide (415 mg) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.64 ml) were added,

followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. Dichloromethane was added to the residue and the resulting mixture was washed successively with 1N hydrochloric acid, and saturated aqueous NaCl solution. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (Φ 3.0 x 10.0 cm, dichloromethane : methanol = 100:1), whereby the title compound (518 mg, 44%) was obtained as colorless foam.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.33(9H,s), 2.23-2.60(3H,m), 2.62-2.78(1H,m), 3.05(1H,br s), 3.21(3H,s), 3.52-3.70(2H,m), 3.84-3.97(1H,m), 4.56(1H,br s), 7.02(1H,s), 7.32(1H,d,J=8.8Hz), 7.49(1H,J=8.8Hz), 7.77(1H,s), 11.84(1H,s), 12.43(1H,s).

MS (FAB) m/z : 557 $[(M+Na)^+, Cl^{35}]$, 559 $[(M+Na)^+, Cl^{37}]$.

[Referential Example 477] 1-[(5-Chloroindol-2-yl)sulfonyl]-3-[(N-methyl-N-

methylsulfonylcarbamoyl)methyl]piperazine trifluoroacetate

In N,N-dimethylformamide (10 ml) was dissolved 1-tert-butoxycarbonyl-4-[(5-chloroindol-2-yl)sulfonyl]-2-[(N-methylsulfonylcarbamoyl)methyl]piperazine (347 mg), followed by the addition of sodium bicarbonate (55 mg) and methyl iodide (0.05 ml). The resulting mixture was stirred overnight at room temperature. The reaction mixture was

then concentrated under reduced pressure. Dichloromethane was added to the residue and the resulting mixture was washed successively with water and saturated aqueous NaCl solution, each once. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (Φ 1.7 x 12.0 cm, dichloromethane : methanol = 200:1), whereby the title compound was obtained as colorless foam. The resulting foam was dissolved in dichloromethane (1 ml), followed by the addition of trifluoroacetic acid (2 ml). After the resulting mixture was stirred at room temperature for 1 minute, the reaction mixture was concentrated under reduced pressure. Diethyl ether was added to the residue and the precipitate so formed was collected by filtration, whereby the title compound (189 mg, 43%) was obtained as colorless foam.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.60-2.80 (2H,m), 3.02-3.11 (2H,m), 3.16 (3H,s), 3.20-3.30 (1H,m), 3.39 (3H,s), 3.61-3.80 (4H,m), 7.08 (1H,d,J=1.5Hz), 7.34 (1H,dd,J=8.8,2.0Hz), 7.50 (1H,J=8.8Hz), 7.80 (1H,d,J=2.2Hz), 12.54 (1H,br s).
 MS (FAB) m/z : 449 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 451 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Referential Example 478] N-methanesulfonylhydrazine hydrochloride

In pyridine (30 ml) was dissolved t-butyl carbazate (2.64 g), followed by the addition of methanesulfonyl chloride (1.62 ml) under ice cooling. The resulting mixture was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue and the resulting mixture was washed successively with 1N hydrochloric acid and a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was solidified by the addition of hexane and ethyl acetate, whereby a pale yellow solid was obtained. The solid was dissolved in dichloromethane (20 ml), followed by the addition of saturated solution of hydrochloride in ethanol (20 ml). The resulting mixture was then concentrated under reduced pressure. The residue was solidified by the addition of ethyl acetate, whereby N-methanesulfonylhydrazine (1.67 g, 57%) was obtained as a pale yellow solid.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.25(3H,s), 9.80(br s,9.80).

MS (FAB) m/z : 111 ($\text{M}+\text{H}$) $^+$.

[Referential Example 479] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(2-methylsulfonylhydrazino)carbonylmethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine trifluoroacetate

In dichloromethane (20 ml) were dissolved 1-tert-butoxycarbonyl-2-carboxymethyl-4-[(5-chloroindol-2-yl)sulfonyl]piperazine (600 mg), N-methanesulfonylhydrazine (192 mg), 1-hydroxybenzotriazole monohydrate (200 mg) and 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (301 mg), followed by the addition of triethylamine (0.21 ml). The resulting mixture was stirred overnight at room temperature. The reaction mixture was then concentrated under reduced pressure. Ethyl acetate was added to the residue and the resulting mixture was washed with water and saturated aqueous NaCl solution, each once. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (Φ 3.0 x 8.0 cm, dichloromethane : methanol = 50:1), whereby colorless foam was obtained. The resulting foam was dissolved in dichloromethane (2 ml), followed by the addition of trifluoroacetic acid (10 ml). After the resulting mixture was stirred at room temperature for 1 minute, the reaction mixture was concentrated under reduced pressure. Diethyl ether was added to the residue and the precipitate so formed was collected by filtration, whereby the title compound (278 mg, 38%) was obtained as colorless foam.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.51-2.82 (3H,m), 2.96 (3H,s), 3.11-3.21 (1H,m), 3.31-3.42 (1H,m), 3.60-3.85 (4H,m), 7.07 (1H,s),

7.34 (1H, dd, J=8.8, 2.0 Hz), 7.50 (1H, J=8.8 Hz), 7.80 (1H, s),
 9.52 (1H, d, J=2.7 Hz), 10.39 (1H, d, J=2.7 Hz), 12.51-12.57 (1H, m).
 MS (FAB) m/z: 450 [(M+H)⁺, Cl³⁵], 452 [(M+H)⁺, Cl³⁷].

[Referential Example 480] 1-(tert-Butoxycarbonyl)-4-[(5-
 5 chloroindol-2-yl)sulfonyl]-2-[(pyrrolidin-1-
 ylcarbonyl)methyl]piperazine

The title compound was obtained by employing the
 method of Referential Example 319 in which 1-(3-
 dimethylaminopropyl-3-ethylcarbodiimide hydrochloride had
 10 been used as a condensing agent.

¹H-NMR (CDCl₃) δ: 1.41 (9H, s), 1.85-1.97 (2H, m), 1.98-
 2.18 (2H, m), 2.22-2.35 (1H, m), 2.50-3.00 (3H, m),
 2.97 (1H, dt, J=3.4, 13.0 Hz), 3.40-3.60 (4H, m), 3.64-3.75 (1H, m),
 3.80-4.20 (2H, m), 4.63 (1H, br d, J=10.0 Hz),
 15 6.96 (1H, d, J=1.7 Hz), 7.27 (1H, dd, J=9.1, 1.7 Hz),
 7.37 (1H, d, J=9.1 Hz), 7.65 (1H, d, J=1.7 Hz).

MS (FAB) m/z: 511 [(M+H)⁺, Cl³⁵], 513 [(M+H)⁺, Cl³⁷].

[Referential Example 481] 2-[(N-Benzylcarbonyl)methyl]-1-
 (tert-butoxycarbonyl)-4-[(5-chloroindol-2-
 20 yl)sulfonyl]piperazine

The title compound was obtained by employing the
 method of Referential Example 319 in which 1-(3-
 dimethylaminopropyl-3-ethylcarbodiimide hydrochloride had
 been used as a condensing agent.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.40 (9H, s), 2.35-2.48 (1H, m), 2.50-2.85 (3H, m), 2.95-3.07 (1H, m), 3.62-3.78 (1H, m), 3.80-4.15 (2H, m), 4.40-4.50 (2H, m), 4.60-4.70 (1H, m), 6.93 (1H, s), 7.20-7.40 (7H, m), 7.64 (1H, s).

5 MS (FAB) m/z : 547 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 549 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Referential Example 482] 5(6)-chloro-2-mercaptobenzimidazole

Carbon disulfide (6.60 ml) and sodium hydroxide (6.330 g) were added to the mixture of 4-chloro-1,2-phenylenediamine (14.37 g), ethanol (100 ml) and water (15 ml), and reacted under reflux for 3 hours. The reaction mixture was added by active carbon (4.0 g), refluxed for 10 minutes, and filtrated by means of suction. The precipitated substances were washed with ethanol (100 ml) and 70°C hot water (200 ml) to obtain a solution. The obtained solution was added to the mixture of acetic acid (9.0 ml) and water (16.0 ml), concentrated under reduced pressure, purified by chromatography on a silica gel column (ethyl acetate), and solidified by acetone-water and ethyl acetate-hexane, followed by drying. Thus, the title compound (9.03 g) was obtained as pale yellow powder.

m.p. >220°C (dec)

IR (KBr) cm^{-1} 3116, 3084, 3055, 2952, 1614, 1512, 1475, 1369, 1323, 1190, 1066.

25 $^1\text{H-NMR}$ (CD_3OD) δ 7.15 (2H, s), 7.21 (1H, s).

MS (EI) m/z 184 [M^+ , C^{135}], 186 [M^+ , C^{137}].

[Referential Example 483] 1-(tert-butoxycarbonyl)-4-
[[5(6)-chlorobenzimidazol-2-yl]sulfonyl]piperazine

5 5(6)-chloro-2-mercaptobenzimidazole (1.837 g) was
suspended in a 20% solution of acetic acid, and then blown
by a chloride gas at a temperature less than 7°C for 70
minutes. Yellow precipitates were obtained by filtration
and thereafter, washed with cold water. The obtained
yellow solid was added to the mixture of 1-(tert-
10 butoxycarbonyl)piperazine (3.905 g), water (18 ml) and
acetone (20 ml), and stirred at room temperature for 20
hours. After discarding the acetone, precipitates were
filtered and dried, whereby the title compound (3.16 g) was
obtained as pale yellow powder.

15 m.p. $210-211^{\circ}\text{C}$

IR (KBr) cm^{-1} 3212, 2983, 1666, 1435, 1367, 1356, 1279,
1176, 1165, 1147, 1138, 974, 949.

$^1\text{H-NMR}$ (CDCl_3) δ 1.44 (9H, s), 3.33-3.41 (4H, m), 3.53-3.59
(4H, m), 7.30-7.60 (2H, m), 7.72-7.88 (1H, m).

20 MS (FAB) m/z 401 [$(M^+ + H)^+$, C^{135}], 403 [$(M^+ + H)^+$, C^{137}].

[Referential Example 484] 1-[[5(6)-chlorobenzimidazol-2-
yl]sulfonyl]piperazine hydrochloride

Saturated solution of hydrochloride in ethanol (5.0
ml) was added to the mixture of 1-(tert-butoxycarbonyl)-4-
25 [[5(6)-chlorobenzimidazol-2-yl]sulfonyl]piperazine (1.406

g), ethanol (5.0 ml) and dichloromethane (4.0 ml), and then stirred at room temperature for 4 hours. After concentration under reduced pressure, the obtained product was purified by chromatography on a silica gel column (dichloromethane:methanol = 20:1). The purified compound was added to 1N solution of hydrochloride in ethanol (1 ml), concentrated and dried, whereby the title compound (1.19 g) was obtained as a hygroscopic colorless amorphous substance.

$^1\text{H-NMR}$ (DMSO-d_6) δ 3.25-3.80 (8H, m), 7.40-7.50 (1H, br), 7.60-7.80 (2H, br), 9.20-9.55 (1H, br).

MS (FAB) m/z 301 $[(M + H)^+, C^{135}]$, 303 $[(M + H)^+, C^{137}]$.

[Example A-1] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

At room temperature, 1-[4-(4-pyridyl)benzoyl]piperazine ditrifluoroacetate (1.19 g) was suspended in dichloromethane (100 ml), followed by the addition of diisopropylethylamine (1.68 ml) and 6-chloro-2-naphthylsulfonyl chloride (WO/96/10022) (691 mg). After stirring at room temperature for 2 hours, the reaction mixture was purified by chromatography on a silica gel column (2% methanol - dichloromethane). To the resulting fraction, 1N hydrochloric acid in ethanol was added to make it weakly acidic. The solvent was then distilled off. The resulting colorless solid was washed with tetrahydrofuran,

whereby the title compound (1.05 g, 81%) was obtained as a colorless solid.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.95-3.25 (4H, m), 3.43 (2H, br s),
3.60 (2H, br s), 7.56 (2H, d, $J=8.3\text{Hz}$), 7.74 (1H, dd, $J=8.8, 2.5\text{Hz}$),
5 7.83 (1H, dd, $J=8.8, 2.0\text{Hz}$), 8.01 (2H, d, $J=8.3\text{Hz}$),
8.19 (1H, d, $J=8.8\text{Hz}$), 8.25-8.40 (4H, m), 8.51 (1H, s),
8.94 (2H, d, $J=6.8\text{Hz}$).

MS (FAB) m/z : 492 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 494 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{26}\text{H}_{22}\text{N}_3\text{O}_3\text{ClS}\cdot\text{HCl}\cdot 0.5\text{H}_2\text{O}$

10 Calculated: C, 58.10; H, 4.50; N, 7.82; Cl, 13.19; S, 5.97.

Found: C, 58.12; H, 4.67; N, 7.66; Cl, 13.12; S, 6.10.

[Example A-2] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

15 In dichloromethane (30 ml), 4-tert-butoxycarbonyl-2-ethoxycarbonyl-1-[4-(4-pyridyl)benzoyl]piperazine (514 mg) was dissolved, followed by the addition of trifluoroacetic acid (30 ml) under ice cooling. After stirring at room temperature for 45 minutes, the residue obtained by
20 distilling off the solvent was suspended in dichloromethane (100 ml) under ice cooling, followed by the addition of diisopropylethylamine (1.02 ml) and 6-chloro-2-naphthylsulfonyl chloride (W096/10022) (366 mg). After stirring at room temperature for one hour, the reaction
25 mixture was purified as was by chromatography on a silica gel column (1% methanol - dichloromethane). To the

resulting fraction, 1N hydrochloric acid in ethanol was added to make it weakly acidic. The solvent was then distilled off. The resulting colorless solid was washed with ethanol, whereby the title compound (308 mg, 43%) was obtained as a colorless solid.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.15-1.30 (3H,m), 2.60-5.40 (9H,m), 7.50 (2/3H,d,J=8.3Hz), 7.57 (4/3H,d,J=7.8Hz), 7.74 (1H,dd,J=9.0,1.7Hz), 7.83 (1H,d,J=8.8Hz), 8.00 (2/3H,d,J=7.8Hz), 8.04 (4/3H,d,J=8.3Hz), 8.19 (1H,d,J=8.8Hz), 8.25-8.35 (4H,m), 8.55 (1H,s), 8.92 (2H,d,J=4.9Hz).

MS (FAB) m/z : 564 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 566 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{29}\text{H}_{26}\text{N}_3\text{O}_5\text{ClS}\cdot\text{HCl}\cdot 0.5\text{H}_2\text{O}$

Calculated: C, 57.15; H, 4.63; N, 6.89; Cl, 11.63; S, 5.26.

Found: C, 56.95; H, 4.68; N, 6.70; Cl, 11.36; S, 5.30.

[Example A-3]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine-2-carboxylic acid hydrochloride

In a mixed solvent of ethanol (1 ml), tetrahydrofuran (1 ml) and water (1 ml), 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride (152 mg) obtained in Example A-2 was dissolved under ice cooling, followed by the dropwise addition of a 1N aqueous solution of sodium hydroxide. The reaction mixture was stirred at room temperature for 90 minutes. After concentration under

reduced pressure, 1N hydrochloric acid was added to the reaction mixture to make it weakly acidic. The colorless solid so precipitated was collected by filtration, followed by drying, whereby the title compound (62 mg, 42%) was
 5 obtained as a colorless solid.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.65-5.30 (7H, m), 7.49 (4/5H, d, $J=7.7\text{Hz}$),
 7.56 (6/5H, d, $J=8.3\text{Hz}$), 7.74 (1H, dd, $J=8.8, 2.0\text{Hz}$),
 7.82 (1H, d, $J=8.3\text{Hz}$), 7.95-8.05 (2H, m), 8.19 (1H, d, $J=8.3\text{Hz}$),
 8.20-8.35 (4H, m), 8.53 (1H, s), 8.92 (2H, d, $J=5.4\text{Hz}$).

10 MS (FAB) m/z : 536 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 538 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{27}\text{H}_{22}\text{N}_3\text{O}_5\text{ClS}\cdot 0.9\text{HCl}\cdot 1.2\text{H}_2\text{O}$

Calculated: C, 54.92; H, 4.32; N, 7.12; Cl, 11.41; S, 5.43.

Found: C, 54.94; H, 4.42; N, 6.83; Cl, 11.31; S, 5.33.

[Example A-4]

15 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)nicotinyll]piperazine hydrochloride

In dichloromethane (10 ml), 6-(4-pyridyl)nicotinic acid hydrochloride (96 mg) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine trifluoroacetate (150 mg) were
 20 suspended, followed by the addition of 1-hydroxybenzotriazole (48 mg) and N-methylmorpholine (155 μl). After the addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (102 mg) under ice cooling, the resulting mixture was stirred at room temperature for
 25 16 hours. Owing to the slow reaction, N,N-dimethylformamide (10 ml) was added to the reaction mixture

and the resulting mixture was stirred for 3 days. After completion of the reaction, the solvent was distilled off. The residue was purified by chromatography on a silica gel column (1% methanol - dichloromethane). The solvent was then distilled off. To the residue, tetrahydrofuran and 1N hydrochloric acid in ethanol were added and the solid so precipitated was collected by filtration and dried, whereby the title compound (105 mg, 55%) was obtained as a colorless solid.

¹H-NMR (DMSO-d₆) δ: 3.00-3.25(4H,m), 3.46(2H,br s), 3.76(2H,br s), 7.74(1H,dd,J=8.5,1.7Hz), 7.83(1H,d,J=8.8Hz), 8.07(1H,dd,J=7.8,1.5Hz), 8.19(1H,d,J=8.8Hz), 8.28(1H,s), 8.29(1H,d,J=8.8Hz), 8.42(1H,d,J=8.3Hz), 8.51(1H,s), 8.65(2H,d,J=6.4Hz), 8.80(1H,m), 9.01(2H,d,J=5.9Hz).
MS (FAB) m/z: 493 [(M+H)⁺, Cl³⁵], 495 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₅H₂₁N₄O₃ClS·HCl·H₂O

Calculated: C, 54.85; H, 4.42; N, 10.23; Cl, 12.95; S, 5.86.

Found: C, 54.57; H, 4.51; N, 10.06; Cl, 13.08; S, 5.87.

[Example A-5] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-3-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was conducted using 4-(3-pyridyl)benzoic acid hydrochloride and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

trifluoroacetate as starting materials, whereby the title compound was obtained as a colorless solid.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.00-3.25 (4H, m), 3.47 (2H, br s),
3.73 (2H, br s), 7.51 (2H, d, $J=8.3\text{Hz}$), 7.73 (1H, dd, $J=8.8, 2.0\text{Hz}$),
5 7.8-7.9 (3H, m), 7.92 (1H, dd, $J=7.8, 5.4\text{Hz}$), 8.19 (1H, d, $J=8.8\text{Hz}$),
8.25-8.30 (2H, m), 8.50 (1H, s), 8.55-8.65 (1H, m), 8.75-
8.85 (1H, m), 9.14 (1H, d, $J=2.0\text{Hz}$).

MS (FAB) m/z : 492 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 494 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{26}\text{H}_{22}\text{N}_3\text{O}_3\text{ClS}\cdot 0.85\text{HCl}\cdot \text{H}_2\text{O}$

10 Calculated: C, 57.72; H, 4.63; N, 7.77; Cl, 12.12; S, 5.93.

Found: C, 57.44; H, 4.62; N, 7.68; Cl, 11.99; S, 5.83.

[Example A-6] 4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In dichloromethane (10 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine (300 mg)
15 obtained in Example A-1 was dissolved, followed by the addition of 3-chloroperbenzoic acid (382 g) at -20°C . The resulting mixture was stirred at -20°C for 21 hours. An aqueous solution of sodium sulfite was added to decompose
20 an excess peroxide. Dichloromethane and a saturated aqueous solution of sodium bicarbonate were added to separate an organic layer. After drying the organic layer over anhydrous magnesium sulfate, the residue obtained by distilling off the solvent was purified by chromatography
25 on a silica gel column (2-5% methanol - dichloromethane). After the solvent was distilled off, ether was added to the

residue to solidify it, followed by collection through filtration, whereby the title compound (200 mg, 63%) was obtained as a colorless solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.90-3.40 (4H,m), 3.40-4.20 (4H,m),
 5 7.43 (2H,d,J=8.3Hz), 7.47 (2H,d,J=7.3Hz), 7.55-7.65 (3H,m),
 7.76 (1H,dd,J=8.8,1.5Hz), 7.90-8.00 (3H,m),
 8.26 (2H,d,J=7.3Hz), 8.31 (1H,s).

MS (FAB) m/z : 508 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 510 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{26}\text{H}_{22}\text{N}_3\text{O}_4\text{ClS}\cdot 0.8\text{H}_2\text{O}$

10 Calculated: C, 59.78; H, 4.55; N, 8.04; Cl, 6.79; S, 6.14.

Found: C, 59.82; H, 4.45; N, 7.94; Cl, 6.85; S, 6.29.

[Example A-7] 1-[4-(2-Aminopyridin-5-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In a mixed solvent of dichloromethane (1 ml) and
 15 ethanol (1 ml), 1-[4-[2-tert-butoxycarbonylamino]pyridin-5-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine
 (128 mg) was dissolved, followed by the addition of a
 saturated hydrochloride solution in ethanol (10 ml) under
 ice cooling. After stirring at room temperature for 1
 20 minute, the solvent was distilled off. Isopropanol was
 added to the residue for crystallization. The crystals so
 obtained were collected by filtration and dried, whereby
 the title compound (88 mg, 68%) was obtained as a colorless
 solid.

¹H-NMR (DMSO-d₆) δ: 3.00-3.20 (4H,m), 3.30-3.90 (4H,m),
 7.05 (1/2H,d,J=8.8Hz), 7.06 (1/2H,d,J=8.8Hz),
 7.43 (2H,d,J=8.3Hz), 7.67 (2H,d,J=8.3Hz), 7.73 (1H,d,J=8.3Hz),
 7.82 (1H,d,J=8.8Hz), 7.90-8.10 (2H,br), 8.18 (1H,d,J=8.3Hz),
 8.25-8.35 (4H,m), 8.50 (1H,s).

MS (FAB) m/z: 507 [(M+H)⁺, Cl³⁵], 509 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₂₃ClN₄O₃S·HCl·1.2H₂O·0.8iPrOH

Calculated: C, 55.56; H, 5.52; N, 9.13; Cl, 11.55; S, 5.22.

Found: C, 55.40; H, 5.24; N, 8.85; Cl, 11.79; S, 5.50.

[Example A-8] 1-[4-(4-Aminophenyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example A-7, a reaction was conducted using 1-[4-[4-(tert-butoxycarbonylamino)phenyl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material, whereby the title compound was obtained as a colorless solid.

¹H-NMR (DMSO-d₆) δ: 2.90-3.20 (4H,m), 3.25-3.80 (4H,m),
 6.68 (2H,d,J=8.3Hz), 7.32 (2H,d,J=8.3Hz), 7.39 (2H,d,J=8.3Hz),
 7.54 (2H,d,J=8.3Hz), 7.73 (1H,dd,J=8.8,2.0Hz),
 7.82 (1H,dd,J=8.8,2.0Hz), 8.18 (1H,dd,J=8.8Hz), 8.25-8.40 (2H,m), 8.50 (1H,br s).

MS (FAB) m/z: 506 [(M+H)⁺, Cl³⁵], 508 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₇H₂₄ClN₃O₃S·0.2HCl

Calculated: C, 63.18; H, 4.75; N, 8.19; Cl, 8.29; S, 6.25.

Found: C, 62.93; H, 4.93; N, 7.91; Cl, 7.99; S, 6.36.

[Example A-9] 1-[4-(2-Aminothiazol-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was effected using 4-(2-aminothiazol-4-yl)benzoic acid and 1-
 5 [(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.90-3.20 (4H,m), 3.30-3.90 (4H,m),
 7.26 (1H,s), 7.41 (2H,d,J=8.3Hz), 7.73 (1H,dd,J=8.8,2.0Hz),
 10 7.79 (2H,d,J=8.3Hz), 7.82 (1H,dd,J=8.8,2.0Hz),
 8.18 (1H,d,J=8.8Hz), 8.25-8.30 (2H,m), 8.50 (1H,br s).
 MS (FAB) m/z: 513 [(M+H)⁺, Cl³⁵], 515 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₁N₄O₃ClS₂·HCl·0.3H₂O

Calculated: C, 51.95; H, 4.11; N, 10.10; Cl, 12.78; S,
 15 11.56.

Found: C, 51.99; H, 4.19; N, 10.03; Cl, 12.61; S,
 11.45.

[Example A-10] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-[imidazol-4(5)-yl]benzoyl]piperazine hydrochloride

20 In dichloromethane (5 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-[1-triphenylmethylimidazol-4(5)-yl]benzoyl]piperazine (303 mg) was dissolved, followed by the addition of a saturated hydrochloride solution in ethanol (30 ml) under ice cooling. After stirring at room
 25 temperature for 3 hours, the solvent was distilled off.
 Ether was added to the residue for crystallization and the

resulting crystals were collected by filtration, whereby the title compound (307 mg, 76%) was obtained as a colorless solid.

¹H-NMR (DMSO-d₆) δ: 2.90-3.20 (4H,m), 3.30-3.90 (4H,m),
 5 7.47 (2H,d,J=8.3Hz), 7.74 (1H,dd,J=8.8,2.0Hz),
 7.82 (1H,dd,J=8.8,2.0Hz), 7.89 (2H,d,J=8.3Hz),
 8.19 (1H,d,J=8.8Hz), 8.22 (1H,d,J=1.0Hz), 8.25-8.30 (2H,m),
 8.50 (1H,m), 9.22 (1H,d,J=1.0Hz).

MS (FAB) m/z: 481 [(M+H)⁺, Cl³⁵], 483 [(M+H)⁺, Cl³⁷].

10 Elementary analysis for C₂₄H₂₁ClN₄O₃S·HCl·0.4H₂O

Calculated: C, 54.94; H, 4.38; N, 10.68; Cl, 13.52; S, 6.11.

Found: C, 54.98; H, 4.29; N, 10.62; Cl, 13.56; S, 6.14.

15 [Example A-11] 1-[4-(2-Aminoimidazol-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was conducted using 4-[2-aminoimidazol-4-yl]benzoic acid hydrochloride and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials,
 20 whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.90-3.20 (4H,m), 3.30-3.90 (4H,m),
 7.39 (2H,d,J=8.3Hz), 7.47 (1H,s), 7.49 (2H,br s),
 7.67 (2H,d,J=8.3Hz), 7.73 (1H,dd,J=8.8,2.5Hz),

7.82 (1H, dd, J=8.8, 2.0 Hz), 8.18 (1H, d, J=8.8 Hz), 8.25-
8.30 (2H, m), 8.50 (1H, br s).

MS (FAB) m/z: 496 [(M+H)⁺, Cl³⁵], 498 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₂N₅O₃ClS·HCl

5 Calculated: C, 54.14; H, 4.35; N, 13.15; Cl, 13.32; S,
6.02.

Found: C, 53.94; H, 4.39; N, 12.82; Cl, 13.27; S,
6.07.

[Example A-12] 4-[4-[[4-[(6-Chloronaphthalen-2-
10 yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-1-
methylpyridinium iodide

In a mixed solvent of benzene (10 ml) and methanol (10
ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-
yl)benzoyl]piperazine (300 mg) obtained in Example A-1 was
15 dissolved at room temperature, followed by the addition of
methyl iodide (1 ml). To the resulting mixture, the same
amount of methyl iodide was added three times at intervals
of 24 hours, followed by heating under reflux for 4 days.
The reaction mixture was distilled under reduced pressure
20 and the residue was washed with methanol, collected by
filtration and dried, whereby the title compound (229 mg,
58%) was obtained as a yellow solid.

¹H-NMR (DMSO-d₆) δ: 3.03 (2H, br s), 3.13 (2H, br s),
3.43 (2H, br s), 3.75 (2H, br s), 4.34 (3H, s),
25 7.59 (2H, d, J=8.8 Hz), 7.74 (1H, dd, J=8.8, 2.4 Hz),
7.85 (1H, dd, J=8.8, 2.0 Hz), 8.08 (2H, d, J=8.8 Hz),

8.19 (1H, d, J=8.8Hz), 8.25-8.30 (2H, m), 8.45-8.55 (3H, m),
9.03 (2H, d, J=6.8Hz).

Elementary analysis for $C_{27}H_{25}N_3O_3ClIS \cdot H_2O$

Calculated: C, 49.74; H, 4.17; N, 6.45.

5 Found: C, 49.60; H, 4.09; N, 6.23.

[Example A-13] 3-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, a reaction was
conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-
10 (pyridin-3-yl)benzoyl]piperazine, which had been obtained
in Example A-5, as a starting material, whereby the title
compound was obtained.

1H -NMR ($CDCl_3$) δ : 2.90-3.40 (4H, m), 3.40-4.20 (4H, m), 7.50-
7.60 (1H, m), 7.40-7.45 (3H, m), 7.54 (2H, d, J=8.3Hz),
15 7.60 (1H, dd, J=8.8, 2.0Hz), 7.76 (1H, dd, J=8.8, 2.0Hz), 7.90-
8.00 (3H, m), 8.22 (1H, d, J=5.9Hz), 8.31 (1H, d, J=2.0Hz),
8.43 (1H, br s).

MS (FAB) m/z: 508 $[(M+H)^+, Cl^{35}]$, 510 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{26}H_{22}N_3O_4ClS \cdot H_2O$

20 Calculated: C, 59.37; H, 4.60; N, 7.99; Cl, 6.74; S, 6.10.

Found: C, 59.48; H, 4.69; N, 7.74; Cl, 6.73; S, 6.07.

[Example A-14] 1-[2-Carboxy-4-(pyridin-4-yl)benzoyl]-4-
[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In dichloromethane (50 ml), 1-[2-tert-butoxycarbonyl-
25 4-(pyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (250 g) was dissolved,

followed by the dropwise addition of trifluoroacetic acid (50 ml) under ice cooling. After stirring at room temperature for 5 hours, the solvent was distilled off. The residue was dissolved in methanol and the resulting solution was allowed to stand in a refrigerator for one day. The colorless solid so precipitated was collected by filtration and dried, whereby the title compound (550 mg, 28%) was obtained as a colorless solid.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.90-3.40 (6H,m), 3.65-3.75 (2H,m), 7.41 (1H,d,J=7.8Hz), 7.70-7.75 (3H,m), 7.82 (1H,dd,J=8.8,2.0Hz), 8.00 (1H,dd,J=7.8,1.5Hz), 8.15-8.30 (4H,m), 8.50 (1H,br s), 8.67 (2H,d,J=5.9Hz), 13.29 (1H,br s).

MS (FAB) m/z : 536 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 538 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{27}\text{H}_{22}\text{ClN}_3\text{O}_5\text{S}\cdot 0.5\text{H}_2\text{O}$

Calculated: C, 59.50; H, 4.25; N, 7.71; Cl, 6.50; S, 5.88.

Found: C, 59.54; H, 4.30; N, 7.37; Cl, 6.35; S, 5.89.

[Example A-15] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)thiophen-2-yl]carbonyl]piperazine

hydrochloride

In the same manner as in Example A-4, a reaction was conducted using 5-(pyridin-4-yl)thiophene-2-carboxylic acid hydrochloride obtained in Referential Example 28 and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.11(4H, br s), 3.74(4H, br s),
 7.52(1H, d, J=3.9Hz), 7.73(1H, dd, J=8.8, 2.5Hz),
 7.83(1H, dd, J=8.8, 2.0Hz), 8.03(1H, d, J=3.9Hz), 8.10-
 8.15(2H, m), 8.18(1H, d, J=8.8Hz), 8.25-8.30(2H, m),
 5 8.51(1H, s), 8.88(2H, d, J=6.8Hz).

MS (FAB) m/z: 498 [(M+H)⁺, Cl³⁵], 500 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₀ClN₃O₃S₂·HCl·H₂O

Calculated: C, 52.17; H, 4.20; N, 7.61; Cl, 12.83; S,
 11.61.

10 Found: C, 52.04; H, 4.22; N, 7.22; Cl, 12.74; S,
 11.57.

[Example A-16] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
 [[5-(pyridin-4-yl)furan-2-yl]carbonyl]piperazine
 hydrochloride

15 In the same manner as in Example A-4, a reaction was
 conducted using 5-(pyridin-4-yl)furan-2-carboxylic acid
 hydrochloride obtained in Referential Example 29 and 1-[(6-
 chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as
 starting materials, whereby the title compound was
 20 obtained.

¹H-NMR (DMSO-d₆) δ: 3.13(4H, br s), 3.30-4.00(4H, m),
 7.21(1H, d, J=3.9Hz), 7.71(1H, d, J=8.8Hz), 7.75-7.80(1H, m),
 7.83(1H, d, J=8.8 Hz), 8.10-8.30(5H, m), 8.51(1H, s), 8.85-
 8.90(2H, m).

25 MS (FAB) m/z: 482 [(M+H)⁺, Cl³⁵], 484 [(M+H)⁺, Cl³⁷].

Elementary analysis for $C_{24}H_{20}ClN_3O_4S \cdot HCl \cdot H_2O$

Calculated: C, 53.74; H, 4.32; N, 7.83; Cl, 13.22; S, 5.98.

Found: C, 53.51; H, 4.36; N, 7.57; Cl, 13.21; S, 5.97.

[Example A-17] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was conducted using 4-(pyridin-2-yl)benzoic acid hydrochloride obtained in Referential Example 30 and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

1H -NMR (DMSO- d_6) δ : 3.07 (4H, br), 3.60-4.00 (4H, br), 7.46 (3H, br), 7.73 (1H, dd, $J=8.8, 2.0$ Hz), 7.82 (1H, dd, $J=8.8, 2.0$ Hz), 7.94-8.05 (2H, br), 8.08 (2H, d, $J=8.8$ Hz), 8.18 (1H, d, $J=8.8$ Hz), 8.28 (2H, d, $J=8.8$ Hz), 8.50 (1H, s), 8.70 (1H, br).

MS (FAB) m/z : 492 $[(M+H)^+, Cl^{35}]$, 494 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{26}H_{22}ClN_3O_3S \cdot 0.9HCl \cdot H_2O$

Calculated: C, 57.53; H, 4.62; Cl, 12.41; N, 7.74; S, 5.91.

Found: C, 57.55; H, 4.52; Cl, 12.64; N, 7.61; S, 6.03.

[Example A-18] 1-[(E)-4-Chlorostyrylsulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-17, a reaction was conducted using 4-(2-pyridyl)benzoic acid hydrochloride and 1-[(E)-4-chlorostyrylsulfonyl]piperazine hydrochloride as

starting materials, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.19(4H,br), 3.46(2H,br), 3.75(2H,br),
7.36(1H,d,J=15.6Hz), 7.44(1H,d,J=15.6Hz), 7.50-7.58(1H,br),
5 7.53(2H,d,J=7.8Hz), 7.57(2H,d,J=7.8Hz), 7.82(2H,d,J=7.8Hz),
8.13(2H,m), 8.15(2H,d,J=7.8Hz), 8.75(1H,d,J=4.9Hz).

MS (FAB) m/z: 468 [(M+H)⁺, Cl³⁵], 470 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₂ClN₃O₃S·HCl·0.3EtOH·0.3H₂O

Calculated: C, 56.42 H, 4.89; Cl, 13.54; N, 8.02; S, 6.12.

10 Found: C, 56.51 H, 4.83; Cl, 13.46; N, 8.10; S, 5.99.

[Example A-19] 2-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine, which had been obtained
15 in Example A-17, as a starting material, whereby the title compound was obtained.

¹H-NMR (CDCl₃) δ: 3.11(4H,br), 3.63(2H,br), 3.87(2H,br),
7.27(1H,m), 7.33(1H,t,J=8.8Hz), 7.39-7.41(1H,br),
20 7.40(2H,d,J=7.8Hz), 7.60(1H,d,J=8.8Hz), 7.77(1H,d,J=8.8Hz),
7.83(2H,d,J=7.8Hz), 7.93(1H,d,J=3.8Hz), 7.94(1H,s),
8.31(1H,s), 8.33(1H,d,J=5.9Hz).

MS (FAB) m/z: 508 [(M+H)⁺, Cl³⁵], 510 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₂₂ClN₃O₄S

25 Calculated: C, 61.47; H, 4.37; Cl, 6.98; N, 8.27; S, 6.31.

Found: C, 61.32; H, 4.46; Cl, 7.21; N, 8.13; S, 6.02.

[Example A-20] 2-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-1-methylpyridinium iodide

5 In the same manner as in Example A-12, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine, which had been obtained in Example A-17, as a starting material, whereby the title compound was obtained.

10 $^1\text{H-NMR}$ (DMSO- d_6) δ : 2.93-3.23(4H,br), 3.54(2H,br), 3.82(2H,br), 4.30(3H,s), 7.50(2H,d,J=8.8Hz), 7.53(1H,m), 7.70(2H,d,J=8.8Hz), 7.70(1H,br), 7.84-7.92(4H,m), 8.15(1H,t,J=6.8Hz), 8.26(1H,s), 8.52(1H,t,J=6.8Hz), 9.29(1H,d,J=5.9Hz).

15 Elementary analysis for $\text{C}_{27}\text{H}_{25}\text{ClIN}_3\text{O}_3\text{S}\cdot 1.6\text{H}_2\text{O}$

Calculated: C, 48.93; H, 4.29; N, 6.34.

Found: C, 48.81; H, 4.06; N, 6.31.

[Example A-21] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(2,4-diaminopyrimidin-6-yl)benzoyl]piperazine hydrochloride

20 In the same manner as in Example A-4, a reaction was conducted using 4-(2,4-diamino-6-pyrimidyl)benzoic acid hydrochloride and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

25 $^1\text{H-NMR}$ (DMSO- d_6) δ : 3.14(4H,br), 3.45(2H,br s), 3.73(2H,br s), 6.36(1H,s), 7.54(2H,d,J=7.8Hz),

7.74 (1H, dd, J=8.8, 2.0 Hz), 7.82 (1H, d, J=8.8 Hz), 7.83 (1H, s),
 7.84 (2H, d, J=7.8 Hz), 8.18 (1H, J=8.8 Hz), 8.18-8.35 (3H, br),
 8.27 (1H, s), 8.28 (1H, d, J=8.8 Hz), 8.50 (1H, s), 12.64 (1H, br s).
 MS (FAB) m/z: 523 [(M+H)⁺, Cl³⁵], 525 [(M+H)⁺, Cl³⁷].

5 Elementary analysis for C₂₅H₂₃ClN₆O₃S·HCl·1.4H₂O

Calculated: C, 51.36; H, 4.62; Cl, 12.13; N, 14.37; S,
 5.48.

Found: C, 51.38; H, 4.54; Cl, 12.24; N, 14.23; S,
 5.55.

10 [Example A-22] 1-[(E)-4-Chlorostyrylsulfonyl]-4-[4-(2,4-
 diaminopyrimidin-6-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-21, a reaction was
 conducted using 4-(2,4-diamino-6-pyrimidyl)benzoic acid
 hydrochloride and 1-[(E)-4-chlorostyrylsulfonyl]piperazine
 15 hydrochloride obtained in Referential Example 31 as
 starting materials, whereby the title compound was
 obtained.

¹H-NMR (DMSO-d₆) δ: 3.18 (4H, br), 3.43 (2H, br), 3.76 (2H, br),
 4.0 (2H, br), 6.37 (1H, s), 7.84 (2H, d, J=15.6 Hz),
 20 7.44 (1H, J=15.6 Hz), 7.53 (2H, d, J=8.8 Hz), 7.63 (2H, d, J=8.8 Hz),
 7.82 (1H, d, J=8.8 Hz), 7.88 (1H, d, J=8.8 Hz), 8.23 (1H, br s),
 8.32 (1H, br s), 12.58 (1H, br s).

MS (FAB) m/z: 499 [(M+H)⁺, Cl³⁵], 501 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₃H₂₃ClN₆O₃S·1.2HCl·1.4H₂O

25 Calculated: C, 48.64; H, 4.79; Cl, 13.73; N, 14.80; S,
 5.65.

Found: C, 48.46; H, 4.56; Cl, 13.53; N, 14.54; S, 5.72.

[Example A-23] 2-[4-[[4-[(E)-4-Chlorostyrylsulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-1, a reaction was conducted using 2-[4-[(1-piperazyl)carbonyl]phenyl]pyridine N-oxide hydrochloride and (E)-4-chlorostyrylsulfonyl chloride (WO/96/10022) as starting materials, whereby the title compound was obtained.

¹H-NMR (CDCl₃) δ: 3.10-3.40 (4H, br), 3.66 (2H, br), 3.89 (2H, br), 6.65 (1H, d, J=15.6 Hz), 7.28 (1H, m), 7.34 (1H, t, J=7.8 Hz), 7.39-7.48 (6H, m), 7.50 (2H, d, J=7.8 Hz), 7.88 (2H, d, J=7.8 Hz), 8.34 (1H, d, J=5.9 Hz).

MS (FD) m/z: 483 (M⁺, Cl³⁵), 485 (M⁺, Cl³⁷).

Elementary analysis for C₂₄H₂₂ClN₃O₄S·0.5H₂O

Calculated: C, 58.47; H, 4.70; Cl, 7.19; N, 8.52; S, 6.50.

Found: C, 58.49; H, 4.80; Cl, 7.29; N, 8.31; S, 6.34.

[Example A-24] 1-[(E)-4-Chlorostyrylsulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

Under ice cooling, piperazine (727 mg) was dissolved in dichloromethane (10 ml), followed by the addition of (E)-4-chlorostyrylsulfonyl chloride (WO96/10022) (500 mg) in portions. After stirring at room temperature for one hour, the reaction mixture was diluted with dichloromethane (100 ml), washed with a saturated aqueous NaCl solution

solution of sodium bicarbonate, a 5% aqueous solution of citric acid, water and saturated saline and then dried over anhydrous magnesium sulfate. The residue obtained by distilling off the solvent under reduced pressure was suspended in N,N-dimethylformamide (10 ml), followed by the addition of 4-(4-pyridyl)benzoic acid (420 mg) obtained in Referential Example 2 and N,N-dimethyl-4-aminopyridine (309 mg). Under ice cooling, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (405 mg) was added and the resulting mixture was stirred at room temperature for 68 hours. After concentration, the residue was purified by chromatography on a silica gel column (dichloromethane : methanol = 70:1). The colorless solid so obtained was recrystallized from a mixed solvent of ethyl acetate and hexane, followed by recrystallization from ethyl acetate to obtain colorless needle crystals (185 mg). To the filtrate, on the other hand, saturated hydrochloric acid - ethanol (4 ml) was added. After concentration, the residue was recrystallized from methanol - ethyl acetate, whereby the title compound (200 mg) was obtained as colorless needle crystals.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.17(2H, br s), 3.23(2H, br s), 3.48(2H, br s), 3.77(2H, br s), 7.36(1H, d, $J=15.3\text{Hz}$), 7.44(1H, d, $J=15.3\text{Hz}$), 7.53(2H, d, $J=8.8\text{Hz}$), 7.64(2H, d, $J=8.3\text{Hz}$), 7.82(2H, d, $J=8.3\text{Hz}$), 8.06(2H, d, $J=8.8\text{Hz}$), 8.32(2H, d, $J=6.6\text{Hz}$), 8.95(2H, d, $J=6.6\text{Hz}$).

MS (FAB) m/z: 468 [(M+H)⁺, Cl³⁵], 470 [(M+H)⁺, Cl³⁷].

Elementary analysis for

C₂₄H₂₂ClN₃O₃S·HCl·0.2H₂O·0.22CH₃CO₂CH₂CH₃

Calculated: C, 56.66; H, 4.81; Cl, 13.44; N, 7.97; S, 6.08.

5 Found: C, 56.68; H, 4.79; Cl, 13.43; N, 8.04; S, 6.14.

[Example A-25] 4-[4-[[4-[(E)-4-chlorostyrylsulfonyl]piperazin-1-yl]carbonyl]phenyl]-1-methylpyridinium iodide

10 In the same manner as in Example A-12, a reaction was conducted using 1-[(E)-4-chlorostyrylsulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine, which had been obtained in Example A-24, as a starting material, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.04-3.87(8H,br), 4.35(3H,s),
15 7.35(1H,d,J=15.6Hz), 7.44(1H,d,J=15.6Hz),
7.53(2H,d,J=8.3Hz), 7.67(2H,d,J=8.3Hz), 7.82(2H,d,J=8.8Hz),
8.13(2H,d,J=8.3Hz), 8.53(2H,d,J=6.8Hz), 9.05(2H,d,J=7.3Hz).

Elementary analysis for C₂₅H₂₅ClIN₃O₃S·0.5H₂O

Calculated: C, 48.52; H, 4.23; N, 6.79.

20 Found: C, 48.68; H, 4.13; N, 6.41.

[Example A-26] 3-[4-[[4-[(E)-4-chlorostyrylsulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

25 After the protective group was removed by the reaction as in Example A-7, the reaction with (E)-4-chlorostyrylsulfonyl chloride (W096/10022) was effected in

the same manner as in Example A-23, whereby the title compound was obtained.

¹H-NMR (CDCl₃) δ: 3.26(4H,br), 3.52-4.00(4H,br),
6.64(1H,d,J=15.6Hz), 7.45-7.52(7H,m), 7.52(2H,d,J=2.0Hz),
5 7.57(2H,d,J=2.0Hz), 8.22(1H,dt,J=6.3,1.6Hz),
8.44(1H,t,J=1.6Hz).

MS (FAB) m/z: 484 [(M+H)⁺, Cl³⁵], 486 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₂ClN₃O₃S·0.5H₂O

Calculated: C, 58.47; H, 4.70; Cl, 7.19; N, 8.52; S, 6.50.

10 Found: C, 58.49; H, 4.66; Cl, 7.40; N, 8.54; S, 6.56.

[Example A-27] 1-[(E)-4-Chlorostyrylsulfonyl]-4-[4-(pyridin-3-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-17 except for the use, as starting materials, of 4-(3-pyridyl)benzoic acid
15 hydrochloride and 1-[(E)-4-chlorostyrylsulfonyl]piperazine hydrochloride, a reaction was conducted, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.08-3.29(4H,br), 3.42-3.85(4H,br),
7.35(1H,d,J=15.6Hz), 7.43(1H,d,J=15.6Hz),
20 7.52(2H,d,J=8.3Hz), 7.59(2H,d,J=8.3Hz), 7.80-7.93(5H,m),
8.54(1H,d,J=6.8Hz), 8.78(1H,d,J=4.5Hz), 9.13(1H,d,J=2.0Hz).

MS (FAB) m/z: 468 [(M+H)⁺, Cl³⁵], 470 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₂ClN₃O₃S·HCl·1.3H₂O

Calculated: C, 54.61; H, 4.89; N, 7.96; Cl, 13.43; S, 6.07.

25 Found: C, 54.82; H, 4.80; N, 7.91; Cl, 13.14; S, 6.14.

[Example A-28] 3-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-1-methylpyridinium iodide

In the same manner as in Example A-12, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-3-yl)benzoyl]piperazine, which had been obtained in Example A-5, as a starting material, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.50-3.80 (8H, m), 4.44 (3H, s), 7.57 (2H, d, J=8.3Hz), 7.74 (1H, dd, J=8.8, 2.0Hz), 7.84 (1H, dd, J=8.8, 1.5Hz), 7.94 (2H, d, J=8.3Hz), 8.10-8.30 (4H, m), 8.51 (1H, s), 8.90 (1H, d, J=7.8Hz), 9.01 (1H, d, J=5.9Hz), 9.45 (1H, s).

MS (FAB) m/z: 506 [(M+H)⁺, Cl³⁵], 508 [(M+H)⁺, Cl³⁷].

[Example A-29] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[2-hydroxy-4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was conducted using 2-(hydroxy-4-(4-pyridyl)benzoic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.90-3.40 (8H, m), 7.25-7.40 (3H, m), 7.70-7.80 (1H, m), 7.80-7.90 (1H, m), 8.15-8.25 (3H, m), 8.25-8.35 (2H, m), 8.50-8.60 (1H, m), 8.91 (2H, d, J=6.4Hz), 10.41 (1H, br s).

MS (FAB) m/z : 535 $[(M+H)^+, Cl^{35}]$, 537 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{26}H_{22}ClN_3O_4S \cdot 1.1HCl \cdot 1.7H_2O$

Calculated: C, 53.96; H, 4.62; N, 7.26; Cl, 12.86; S, 5.54.

Found: C, 53.62; H, 4.58; N, 7.34; Cl, 13.10; S, 5.94.

5 [Example A-30] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-methoxy-4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was conducted using 3-methoxy-4-(4-pyridyl)benzoic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was
10 obtained.

1H -NMR (DMSO- d_6) δ : 3.00-4.00 (8H, m), 3.81 (3H, s),
7.08 (1H, d, $J=8.8$ Hz), 7.17 (1H, s), 7.55 (1H, d, $J=8.8$ Hz),
7.74 (1H, dd, $J=8.8, 2.0$ Hz), 7.83 (1H, d, $J=8.3$ Hz),
15 8.04 (2H, d, $J=6.3$ Hz), 8.19 (1H, d, $J=8.8$ Hz), 8.25-8.30 (2H, m),
8.52 (1H, s), 8.85 (2H, d, $J=6.3$ Hz).

MS (FAB) m/z : 522 $[(M+H)^+, Cl^{35}]$, 524 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{27}H_{24}ClN_3O_4S \cdot 0.8HCl \cdot 1.7H_2O$

Calculated: C, 55.74; H, 4.89; N, 7.22; Cl, 10.97; S, 5.51.

20 Found: C, 55.59; H, 4.90; N, 7.23; Cl, 10.90; S, 5.52.

[Example A-31] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-hydroxy-4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In dichloromethane (1 ml), boron tribromide (115 μ l) was dissolved, followed by the dropwise addition of a solution of 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[3-methoxy-4-(pyridin-4-yl)benzoyl]piperazine, which had been
25

obtained in Example A-30, in dichloromethane
(dichloromethane: 4 ml) at an external temperature of about
-78°C. While heating gradually to room temperature, the
resulting mixture was stirred for 23 hours. After
5 dichloromethane and water were added to the reaction
mixture and the resulting mixture was stirred for a while,
sodium bicarbonate was added to make alkaline the reaction
mixture, which was separated into an organic layer and a
water layer. From the water layer, another organic layer
10 was extracted with dichloromethane. These organic layers
were combined together, washed with saturated aqueous NaCl
solution and then dried over anhydrous sodium sulfate. The
residue obtained by distilling off the solvent under
reduced pressure was purified by chromatography on a silica
15 gel column (dichloromethane ~ 3% methanol -
dichloromethane). The crudely purified product so obtained
was dissolved in tetrahydrofuran. Solution of
hydrochloride in ethanol was added to the resulting
solution to solidify the same. The resulting solid was
20 collected by filtration and then dissolved in a mixed
solvent of water and methanol. After the removal of the
insoluble matter by filtration, the filtrate was distilled
under reduced pressure, whereby the title compound (36 mg,
30%) was obtained.

25 ¹H-NMR (DMSO-d₆) δ: 3.00-3.80(8H,m), 6.85-6.95(1H,m),
7.01(1H,d,J=1.4Hz), 7.49(1H,d,J=8.8Hz),

7.72 (1H, dd, J=8.8, 2.0 Hz), 7.81 (1H, dd, J=8.5, 1.7 Hz),
 7.94 (2H, d, J=6.4 Hz), 8.19 (1H, d, J=8.8 Hz), 8.25-8.30 (2H, m),
 8.51 (1H, s), 8.75 (2H, d, J=5.9 Hz), 10.67 (1H, s).

MS (FAB) m/z: 508 [(M+H)⁺, Cl³⁵], 510 [(M+H)⁺, Cl³⁷].

5 [Example A-32] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-4-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example A-7, a reaction was effected using 4-tert-butoxycarbonyl-1-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine
 10 as a starting material and the protective group was removed. The residue was then reacted with 4-(4-pyridyl)benzoic acid hydrochloride as in Example A-4, whereby the title compound was obtained.

¹H-NMR (CDCl₃) δ: 0.80-1.10 (3H, m), 3.00-4.00 (8H, m), 4.60-
 15 4.80 (1H, m), 7.42 (2H, d, J=7.8 Hz), 7.47 (2H, d, J=5.9 Hz), 7.50-7.60 (1H, m), 7.64 (2H, d, J=8.3 Hz), 7.70-7.80 (1H, m), 7.85-7.95 (3H, m), 8.33 (1H, s), 8.69 (2H, s).

MS (FAB) m/z: 564 [(M+H)⁺, Cl³⁵], 566 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₉H₂₆ClN₃O₅S·0.3H₂O

20 Calculated: C, 60.78; H, 4.70; N, 7.33; Cl, 6.80; S, 5.60.
 Found: C, 60.84; H, 4.84; N, 6.98; Cl, 7.03; S, 5.70.

[Example A-33] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine-2-carboxylic acid

In the same manner as in Example A-3, the title
 25 compound was obtained using 1-[(6-chloronaphthalen-2-

yl)sulfonyl]-2-ethoxycarbonyl-4-[4-(pyridin-4-yl)benzoyl]piperazine as a starting material.

¹H-NMR (DMSO-d₆) δ: 2.70-5.00 (7H,m), 7.40-7.50 (2H,m), 7.65-7.75 (2H,m), 7.85-8.25 (8H,m), 8.50-8.60 (2H,m), 8.80-8.95 (2H,m).

MS (FAB) m/z: 536 [(M+H)⁺, Cl³⁵], 538 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₇H₂₂ClN₃O₅S·0.3HCl·H₂O

Calculated: C, 57.40; H, 4.34; N, 7.44; Cl, 8.16; S, 5.68.

Found: C, 57.16; H, 4.35; N, 7.36; Cl, 7.92; S, 6.08.

[Example A-34] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[4-(pyridin-3-yl)benzoyl]piperazine

In the same manner as in Example A-2, a reaction was effected, whereby the title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.15-1.30 (3H,m), 2.60-4.60 (8H,m), 5.33 (1H,br), 7.40-7.55 (3H,m), 7.70-7.85 (4H,m), 8.05-8.10 (1H,m), 8.19 (1H,d,J=8.8Hz), 8.25-8.30 (2H,m), 8.50-8.65 (2H,m), 8.91 (1H,s).

MS (FAB) m/z: 564 [(M+H)⁺, Cl³⁵], 566 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₉H₂₆ClN₃O₅S·0.1HCl·0.5H₂O

Calculated: C, 60.40; H, 4.74; N, 7.29; Cl, 6.76; S, 5.56.

Found: C, 60.67; H, 4.61; N, 7.30; Cl, 6.89; S, 5.51.

[Example A-35] 2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-3-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-3, with 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[4-(pyridin-3-yl)benzoyl]piperazine (426 mg) as a starting material, a crude product was obtained by the hydrolysis of the ester, followed by suspension in N,N-dimethylformamide (35 ml). Under ice cooling, di-tert-butyl dicarbonate (646 mg), pyridine (370 μ l) and ammonium bicarbonate (196 mg) were added to the resulting suspension. The resulting mixture was stirred at room temperature for 19 hours. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (4% methanol - dichloromethane) and the eluate was dissolved in tetrahydrofuran. Solution of hydrochloride in ethanol was added to the resulting solution to solidify the same. The resulting solid was collected by filtration and dissolved in a mixed solvent of water and methanol. The insoluble matter was filtered off and the filtrate was distilled under reduced pressure, whereby the title compound (302 mg, 65%) was obtained.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.30-4.50 (6H,m), 5.08 (1H,br), 7.40-7.60 (2H,m), 7.65-7.85 (3H,m), 7.92 (2H,d,J=7.8Hz), 8.00-8.10 (1H,m), 8.20 (2H,d,J=8.8Hz), 8.25-8.35 (2H,m), 8.49 (1H,s), 8.80 (1H,d,J=7.8Hz), 8.88 (1H,d,J=5.4Hz), 9.25 (1H,s).

MS (FAB) m/z : 535 $[(M+H)^+, Cl^{35}]$, 537 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{27}H_{23}ClN_4O_4S \cdot 1.1HCl \cdot 1.7H_2O$

Calculated: C, 53.54; H, 4.58; N, 9.25; Cl, 12.29; S, 5.29.

Found: C, 53.36; H, 4.71; N, 9.07; Cl, 12.17; S, 5.50.

[Example A-36] 2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine
5 hydrochloride

In the same manner as in Example A-35, the title compound was obtained using 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[4-(pyridin-4-yl)benzoyl]piperazine as a starting material.

10 $^1\text{H-NMR}$ (DMSO- d_6) δ : 2.30-2.70 (2H,m), 3.20-3.80 (2H,m), 4.10-4.50 (2H,m), 5.07 (1H,br s), 7.40-7.55 (2H,m), 7.60-7.65 (1H,m), 7.67 (1H,s), 7.72 (1H,dd, $J=8.8, 2.4\text{Hz}$), 7.78 (1H,dd, $J=8.8, 2.4\text{Hz}$), 8.04 (2H,d, $J=8.8\text{Hz}$), 8.20 (1H,d, $J=8.8\text{Hz}$), 8.25-8.35 (4H,m), 8.49 (1H,s),
15 8.95 (2H,d, $J=5.4\text{Hz}$).

MS (FAB) m/z : 535 $[(M+H)^+, \text{Cl}^{35}]$, 537 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{27}\text{H}_{23}\text{ClN}_4\text{O}_4\text{S}\cdot\text{HCl}\cdot 1.8\text{H}_2\text{O}$

Calculated: C, 53.70; H, 4.61; N, 9.28; Cl, 11.74; S, 5.31.

Found: C, 53.87; H, 4.40; N, 8.89; Cl, 11.81; S, 5.23.

20 [Example A-37] 4-[4-[[2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, a reaction was conducted using 2-carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-pyridin-4-yl]benzoyl]piperazine as a
25 starting material, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.30-4.50 (6H,m), 5.04 (1H,br), 7.30-7.90 (10H,m), 8.10-8.30 (5H,m), 8.48 (1H,s).

MS (FAB) m/z: 551 [(M+H)⁺, Cl³⁵], 553 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₇H₂₃ClN₄O₅S·0.8H₂O

5 Calculated: C, 57.35; H, 4.39; N, 9.91; Cl, 6.27; S, 5.67.

Found: C, 57.64; H, 4.50; N, 9.48; Cl, 6.37; S, 5.71.

[Example A-38] 4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

10 In the same manner as in Example A-37, a reaction was conducted, whereby the title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.30-1.40 (3H,m), 2.30-4.70 (8H,m), 5.47 (1H,br s), 7.40-7.80 (8H,m), 7.92 (1H,s), 7.94 (2H,s), 8.26 (2H,d,J=6.8Hz), 8.48 (1H,s).

15 MS (FAB) m/z: 580 [(M+H)⁺, Cl³⁵], 582 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₉H₂₆ClN₃O₆S·1.3H₂O

Calculated: C, 57.72; H, 4.78; N, 6.96; Cl, 5.87; S, 5.31.

Found: C, 57.99; H, 4.75; N, 6.56; Cl, 5.98; S, 5.43.

20 [Example A-39] 4-[4-[[2-Carboxy-4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-3, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.30-4.50 (6H,m), 5.22 (1H,br s), 7.35-7.50 (2H,m), 7.70-7.90 (6H,m), 8.19 (1H,d,J=8.8Hz), 8.25-8.30 (4H,m), 8.53 (1H,s), 13.42 (1H,br).

25

Elementary analysis for $C_{27}H_{22}ClN_3O_6S \cdot 0.2HCl \cdot 1.7H_2O$

Calculated: C, 54.97; H, 4.37; N, 7.12; Cl, 7.21; S, 5.44.

Found: C, 55.07; H, 4.40; N, 6.82; Cl, 7.16; S, 5.47.

[Example A-40] 2-Carbamoyl-4-[(E)-4-chlorostyrylsulfonyl]-
 5 1-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride, and
 2-Carbamoyl-4-[[2-(4-chlorophenyl)-2-ethoxyethyl]sulfonyl]-
 1-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-35, a reaction was
 conducted, whereby the title compounds were obtained.

10 2-Carbamoyl-4-[(E)-4-chlorostyrylsulfonyl]-1-[4-(pyridin-4-
 yl)benzoyl]piperazine hydrochloride

1H -NMR (CD_3OD) δ : 2.80-4.80 (6H,m), 5.32 (1H,br),
 7.04 (1H,d,J=15.6Hz), 7.40-7.50 (3H,m), 7.60-7.80 (4H,m),
 7.95-8.05 (2H,m), 8.20 (2H,br), 8.81 (2H,br).

15 MS (FAB) m/z: 511 $[(M+H)^+, Cl^{35}]$, 513 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{25}H_{23}ClN_4O_4S \cdot 0.9HCl \cdot 1.8H_2O$

Calculated: C, 52.11; H, 4.81; N, 9.72; Cl, 11.69.

Found: C, 52.28; H, 4.83; N, 9.44; Cl, 11.51.

20 2-Carbamoyl-4-[[2-(4-chlorophenyl)-2-ethoxyethyl]sulfonyl]-
 1-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

1H -NMR (CD_3OD) δ : 1.10-1.20 (3H,m), 2.95-4.70 (6H,m),
 5.34 (1H,br), 7.38 (4H,s), 7.65-7.85 (2H,m), 8.05-8.15 (2H,m),
 8.40-8.50 (2H,m), 8.91 (2H,d,J=5.9Hz).

MS (FAB) m/z: 557 $[(M+H)^+, Cl^{35}]$, 559 $[(M+H)^+, Cl^{37}]$.

25 Elementary analysis for $C_{27}H_{29}ClN_4O_5S \cdot HCl \cdot 2.5H_2O$

Calculated: C, 50.78; H, 5.52; N, 8.77; Cl, 11.10; S, 5.02.

Found: C, 50.61; H, 5.38; N, 8.68; Cl, 11.27; S, 5.07.

[Example A-41] 1-[trans-4-(Aminomethyl)cyclohexylmethyl]-
4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine
5 hydrochloride

In the same manner as in Example A-7, a reaction was
conducted, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 0.80-1.00(4H,m), 1.48(1H,m), 1.60-

1.90(5H,m), 2.60(2H,m), 2.90-3.10(4H,m), 3.14(2H,m),

10 3.52(2H,m), 3.77(2H,m), 7.75(1H,dd,J=8.8,2.0Hz),

7.85(1H,d,J=8.8Hz), 7.99(3H,br), 8.21(1H,d,J=8.8Hz), 8.30-

8.40(2H,m), 8.56(1H,s), 10.46(1H,br).

MS (FAB) m/z: 436 [(M+H)⁺, Cl³⁵], 438 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₃₀ClN₃O₂S·2HCl·3/4H₂O

15 Calculated: C, 50.58; H, 6.46; N, 8.04; Cl, 20.36; S, 6.14.

Found: C, 50.74; H, 6.48; N, 7.76; Cl, 20.09; S, 6.19.

[Example A-42] 1-[trans-4-
(Aminomethyl)cyclohexylcarbonyl]-4-[(6-chloronaphthalen-2-
yl)sulfonyl]piperazine hydrochloride

20 In the same manner as in Example A-7, the title
compound was obtained using 1-[trans-4-(N-tert-
butoxycarbonylaminoethyl)cyclohexylcarbonyl]-4-[(6-
chloronaphthalen-2-yl)sulfonyl]piperazine as a starting
material.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 0.90-1.00 (2H,m), 1.20-1.40 (2H,m),
 1.48 (1H,m), 1.50-1.70 (2H,m), 1.70-1.90 (2H,m), 2.44 (1H,m),
 2.59 (2H,m), 2.96 (4H,m), 3.55 (4H,m),
 7.72 (1H,dd, $J=8.8, 2.0\text{Hz}$), 7.81 (1H,d, $J=8.3\text{Hz}$), 7.90 (3H,br),
 5 8.16 (1H,d, $J=8.8\text{Hz}$), 8.20-8.30 (2H,m), 8.49 (1H,s).

MS (FAB) m/z : 450 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 452 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{22}\text{H}_{28}\text{ClN}_3\text{O}_3\text{S}\cdot 0.9\text{HCl}\cdot 1.5\text{H}_2\text{O}$

Calculated: C, 51.83; H, 6.31; N, 8.24; Cl, 13.21; S, 6.29.

Found: C, 51.63; H, 6.22; N, 7.97; Cl, 13.32; S, 6.17.

10 [Example A-43] 1-[N-[trans-4-(Aminomethyl)cyclohexylcarbonyl]glycyl]]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example A-7, a reaction was conducted using 1-[N-[trans-4-(N-tert-

15 butoxycarbonylaminomethyl)cyclohexylcarbonyl]glycyl]]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material, whereby the title compound was obtained.

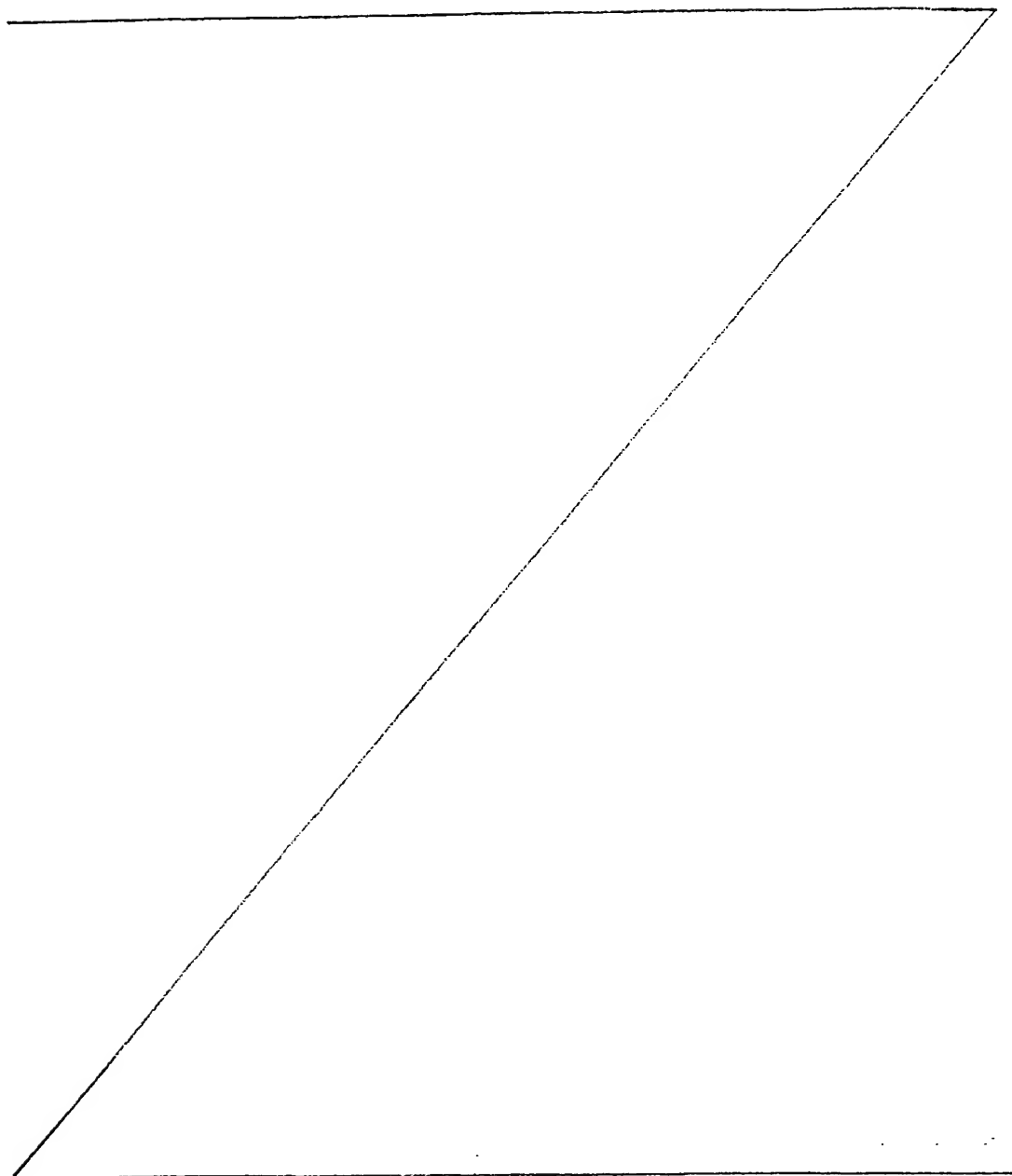
$^1\text{H-NMR}$ (DMSO-d_6) δ : 0.80-1.00 (2H,m), 1.20-1.40 (2H,m),
 1.50 (1H,m), 1.60-1.80 (4H,m), 2.10 (1H,m), 2.62 (2H,m), 2.90-
 20 3.10 (4H,m), 3.40-3.60 (4H,m), 3.83 (2H,d, $J=5.4\text{Hz}$), 7.70-
 7.90 (3H,m), 7.93 (3H,br), 8.17 (1H,d, $J=8.3\text{Hz}$), 8.20-
 8.30 (2H,m), 8.49 (1H,s).

MS (FAB) m/z : 507 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 509 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{24}\text{H}_{31}\text{ClN}_4\text{O}_4\text{S}\cdot \text{HCl}$

Calculated: C, 53.04; H, 5.93; N, 10.31; Cl, 13.05; S,
5.90.

Found: C, 52.90; H, 5.98; N, 10.29; Cl, 12.98; S,
5.91.



[Example A-44] 1-[trans-4-(Aminomethyl)cyclohexylcarbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine hydrochloride

In the same manner as in Example A-7, the title compound was obtained using 1-[trans-4-(N-tert-butoxycarbonylaminoethyl)cyclohexylcarbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine as a starting material.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 0.90-1.10 (2H,m), 1.30-1.50 (2H,m), 1.50-1.90 (7H,m), 2.40-2.80 (3H,m), 3.20-3.70 (8H,m), 7.60-7.70 (1H,m), 7.80-8.00 (4H,m), 8.10-8.20 (1H,m), 8.20-8.30 (2H,m), 8.52 and 8.53 (1H, each s).

MS (FAB) m/z : 464 $[(M+H)^+, \text{Cl}^{35}]$, 466 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{23}\text{H}_{30}\text{ClN}_3\text{O}_3\text{S}\cdot\text{HCl}$

Calculated: C, 55.20; H, 6.24; N, 8.40; Cl, 14.17; S, 6.41.

Found: C, 55.42; H, 6.18; N, 8.26; Cl, 14.11; S, 6.53.

[Example A-45] 1-[4-(Aminomethyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example A-7, the title compound was obtained using 1-[4-(N-tert-butoxycarbonylaminoethyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 3.00-3.20 (4H,br), 3.30-3.80 (4H,br), 4.03 (2H,s), 7.37 (2H,d,J=7.3Hz), 7.50 (2H,d,J=7.3Hz), 7.72 (1H,d,J=8.8Hz), 7.82 (1H,d,J=8.8Hz), 8.18 (1H,d,J=8.8Hz),

8.20-8.40 (2H,m), 8.43 (3H,br), 8.49 (1H,s).

MS (FAB) m/z: 444 [(M+H)⁺, Cl³⁵], 446 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₂₂ClN₃O₃S·HCl·H₂O

Calculated: C, 53.02; H, 5.06; N, 8.43; Cl, 14.23; S, 6.43.

5 Found: C, 53.06; H, 5.30; N, 8.32; Cl, 14.20; S, 6.44.

[Example A-46] 1-[3-(Aminomethyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example A-3, the ester was hydrolyzed using methyl 3-(N-tert-butoxycarbonylaminomethyl)benzoate as a starting material. Reaction was then effected as in Example A-4 or A-7, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.07 (4H,br), 3.20-3.80 (4H,br), 4.00 (2H,s), 7.30-7.60 (4H,m), 7.73 (1H,d,J=8.8Hz), 7.83 (1H,d,J=8.8Hz), 8.10-8.60 (7H,m).

MS (FAB) m/z: 444 [(M+H)⁺, Cl³⁵], 446 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₂₂ClN₃O₃S·HCl·1/4H₂O

Calculated: C, 54.49; H, 4.88; N, 8.67; Cl, 14.62; S, 6.61.

Found: C, 54.64; H, 4.95; N, 8.52; Cl, 14.59; S, 6.70.

20 [Example 47] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-[N-(1-pyrrolin-2-yl)aminomethyl]benzoyl]piperazine hydrochloride

In dimethylformamide (2 ml), 2-methoxy-1-pyrroline (35 mg) was dissolved, followed by the addition of 1-[3-(aminomethyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (0.10 g) and

triethylamine (44 μ l). The resulting mixture was stirred at room temperature for 3 days. After the reaction mixture was concentrated under reduced pressure, the concentrate was diluted with methanol, followed by the addition of 1N
 5 hydrochloric acid. The solvent was then distilled off under reduced pressure. The residue was purified by gel permeation chromatography ("Sephadex LH-20", \varnothing 15 x 300 mm, methanol), followed by solidification in a mixed solvent of methanol and ether, whereby a colorless solid
 10 (0.11 g, 91%) was obtained.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.04 (2H, m), 2.81 (2H, t, $J=7.8\text{Hz}$),
 3.18 (4H, br), 3.20-3.80 (5H, m), 4.10 (1H, br),
 4.51 (2H, d, $J=5.9\text{Hz}$), 7.30-7.50 (4H, m),
 7.72 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.82 (1H, d, $J=8.8\text{Hz}$),
 15 8.18 (1H, d, $J=8.8\text{Hz}$), 8.20-8.30 (2H, m), 8.50 (1H, s),
 10.01 (1H, t, $J=5.9\text{Hz}$), 10.06 (1H, s).

MS (FAB) m/z : 511 $[(M+H)^+, \text{Cl}^{35}]$, 513 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{26}\text{H}_{27}\text{ClN}_4\text{O}_3\text{S} \cdot \text{HCl} \cdot \text{CH}_3\text{OH} \cdot 4/5\text{H}_2\text{O}$

Calculated: C, 54.60; H, 5.70; N, 9.43; Cl, 11.94; S, 5.40.

20 Found: C, 54.84; H, 5.47; N, 9.13; Cl, 11.86; S, 5.48.

[Example A-48] 1-[4-(2-Aminoethyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example A-7, the title compound was obtained using 1-[4-(2-(tert-butoxycarbonylamino)ethyl)benzoyl]-4-[(6-chloronaphthalen-
 25

2-yl)sulfonyl]piperazine as a starting material.

^1H -NMR (DMSO- d_6) δ : 2.90-3.20 (8H,m), 3.40-3.90 (4H,br),
7.28 (4H,s), 7.72 (1H,dd,J=8.8,2.4Hz),
7.81 (1H,dd,J=8.8,2.0Hz), 8.02 (3H,br), 8.17 (1H,d,J=8.3Hz),
8.20-8.30 (2H,m), 8.49 (1H,s).

MS (FAB) m/z : 458 $[(M+H)^+, Cl^{35}]$, 460 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{23}H_{24}ClN_3O_3S \cdot HCl \cdot 1/2CH_3OH \cdot 1/2H_2O$

Calculated: C, 54.34; H, 5.43; N, 8.09; Cl, 13.65; S, 6.17.

Found: C, 54.43; H, 5.26; N, 7.92; Cl, 13.58; S, 6.24.

[Example A-49] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-
[[(3S)-pyrrolidin-3-yl]oxy]benzoyl]piperazine hydrochloride

In the same manner as in Example A-7, the title
compound was obtained using 1-[4-[[(3S)-1-tert-
butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-
chloronaphthalen-2-yl)sulfonyl]piperazine as a starting
material.

^1H -NMR (DMSO- d_6) δ : 2.05-2.25 (2H,m), 3.00-3.10 (4H,m), 3.20-
3.70 (8H,m), 5.16 (1H,br s), 6.95 (2H,d,J=8.8Hz),
7.31 (2H,d,J=8.3Hz), 7.70-7.75 (1H,m),
7.82 (1H,dd,J=8.5,1.7Hz), 8.18 (2H,d,J=8.8Hz), 8.20-
8.30 (2H,m), 8.50 (1H,s).

MS (FAB) m/z : 500 $[(M+H)^+, Cl^{35}]$, 502 $[(M+H)^+, Cl^{37}]$.

[Example A-50] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-
[[(3S)-pyrrolidin-3-yl]oxy]benzoyl]piperazine hydrochloride

In the same manner as in Example 7, the title compound

was obtained using 1-[3-[[[(3S)-1-tert-butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 2.00-2.20 (2H,m), 2.95-3.15 (4H,m), 3.20-3.80 (8H,m), 5.11 (1H,br s), 6.90-6.95 (3H,m), 7.00-7.05 (1H,m), 7.30-7.35 (1H,m), 7.72 (1H,dd, $J=8.8, 2.0\text{Hz}$), 7.81 (1H,dd, $J=8.5, 1.7\text{Hz}$), 8.18 (2H,d, $J=8.8\text{Hz}$), 8.25-8.30 (2H,m), 8.50 (1H,s).

10 MS (FAB) m/z : 500 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 502 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{25}\text{H}_{26}\text{ClN}_3\text{O}_4\text{S}\cdot\text{HCl}\cdot\text{H}_2\text{O}$

Calculated: C, 54.15; H, 5.27; N, 7.58; Cl, 12.79; S, 5.78.

Found: C, 53.84; H, 5.19; N, 7.33; Cl, 12.72; S, 5.86.

[Example A-51] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-
15 [[(3R)-pyrrolidin-3-yl]oxy]benzoyl]piperazine hydrochloride

In the same manner as in Example A-7, the title compound was obtained using 1-[4-[[[(3R)-1-tert-butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting
20 material.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.05-2.25 (2H,m), 3.00-3.10 (4H,m), 3.20-3.70 (8H,m), 5.16 (1H,br s), 6.96 (2H,d, $J=8.8\text{Hz}$), 7.31 (2H,d, $J=8.8\text{Hz}$), 7.74 (1H,dd, $J=8.8, 2.0\text{Hz}$), 7.82 (1H,dd, $J=8.8, 1.5\text{Hz}$), 8.18 (1H,d, $J=8.8\text{Hz}$), 8.25-
25 8.30 (2H,m), 8.50 (1H,s).

MS (FAB) m/z: 500 [(M+H)⁺, Cl³⁵], 502 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₅H₂₆ClN₃O₄S·1.2HCl·0.8H₂O

Calculated: C, 53.80; H, 5.20; N, 7.53; Cl, 13.97; S, 5.74.

5 Found: C, 53.84; H, 5.05; N, 7.51; Cl, 13.79; S, 5.74.

[Example A-52] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-
 [(3R)-pyrrolidin-3-yl]oxy]benzoyl]piperazine hydrochloride

In the same manner as in Example A-7, the title
 compound was obtained using 1-[3-[(3R)-1-tert-
 10 butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-
 chloronaphthalen-2-yl)sulfonyl]piperazine as a starting
 material.

¹H-NMR (DMSO-d₆) δ: 2.00-2.20 (2H, m), 2.95-3.15 (4H, m), 3.20-
 3.80 (8H, m), 5.11 (1H, br s), 6.90-6.95 (2H, m), 7.00-
 15 7.05 (1H, m), 7.30-7.35 (1H, m), 7.74 (1H, dd, J=8.8, 2.0 Hz),
 7.82 (1H, dd, J=8.8, 1.5 Hz), 8.18 (2H, d, J=8.8 Hz), 8.25-
 8.30 (2H, m), 8.50 (1H, s).

MS (FAB) m/z: 500 [(M+H)⁺, Cl³⁵], 502 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₅H₂₆ClN₃O₄S·HCl·H₂O

20 Calculated: C, 54.15; H, 5.27; N, 7.58; Cl, 12.79; S, 5.78.

Found: C, 53.91; H, 5.14; N, 7.37; Cl, 12.62; S, 5.67.

[Example A-53] 1-[4-(2-Aminopyrimidin-5-yl)benzoyl]-4-[(6-
 chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was
 25 conducted using 4-(2-amino-5-pyrimidyl)benzoic acid and 1-
 [(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

as starting materials, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.06(4H,br), 3.56 and (each 2H,br),
4.70-5.45(3H,br), 7.40(2H,d,J=8.8Hz), 7.67(2H,d,J=8.8Hz),
5 7.73(1H,dd,J=8.8,2.0Hz), 7.82(1H,d,J=8.8Hz),
8.18(1H,d,J=8.8Hz), 8.27(1H,s), 8.28(1H,d,J=8.8Hz),
8.50(1H,s), 8.72(1H,s).

MS (FAB) m/z: 508 [(M+H)⁺, Cl³⁵], 510 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₅H₂₂ClN₅O₃S·1.1HCl·0.7H₂O

10 Calculated: C, 53.55; H, 4.40; Cl, 13.28; N, 12.49; S,
5.72.

Found: C, 53.59; H, 4.58; Cl, 13.02; N, 12.58; S,
5.89.

[Example A-54] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
15 [(piperidin-4-yl)acetyl]piperazine hydrochloride

In the same manner as in Example A-7, the title
compound was obtained using 1-[(1-tert-
butoxycarbonylpiperidin-4-yl)acetyl]-4-[(6-
chloronaphthalen-2-yl)sulfonyl]piperazine as a starting
20 material.

¹H-NMR (DMSO-d₆) δ: 1.25(2H,m), 1.71(2H,m), 1.87(1H,m),
2.20(2H,d,J=6.8Hz), 2.78(2H,br), 2.96(4H,br s), 3.14(2H,m),
3.52(4H,br s), 4.02(2H,br), 7.73(1H,dd,J=8.8,2.0Hz),
7.81(1H,d,J=8.8Hz), 8.17(1H,d,J=8.8Hz), 8.28(1H,d,J=8.8Hz),
25 8.26(1H,s), 8.50(1H,s), 8.54(1H,br), 8.75(1H,br).

MS (FAB) m/z : 436 $[(M+H)^+, Cl^{35}]$, 438 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{21}H_{26}ClN_3O_3S \cdot 1.1HCl \cdot 1.1H_2O$

Calculated: C, 50.86; H, 5.96; Cl, 15.01; N, 8.47; S, 6.47.

Found: C, 51.07; H, 5.74; Cl, 14.75; N, 8.36; S, 6.50.

5 [Example A-55] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-(piperidin-4-yl)propionyl]piperazine hydrochloride

In the same manner as in Example A-7, the title compound was obtained using 1-[3-(1-tert-butoxycarbonylpiperidin-4-yl)propionyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

1H -NMR (CD_3OD) δ : 1.29(2H,m), 1.50(1H,m), 1.51(2H,m), 1.89(2H,m), 2.36(2H,m), 2.88(2H,m), 3.08(4H,m), 3.64(4H,m), 4.04(2H,br), 7.58(1H,dd, $J=8.8, 2.0$ Hz), 7.82(1H,dd, $J=8.8, 2.0$ Hz), 8.05(1H,d, $J=8.8$ Hz), 8.06(1H,s), 8.09(1H,d, $J=8.8$ Hz), 8.42(1H,s).

MS (FAB) m/z : 450 $[(M+H)^+, Cl^{35}]$, 452 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{22}H_{28}ClN_3O_3S \cdot 1.8HCl \cdot 0.9H_2O$

Calculated: C, 49.68; H, 5.99; Cl, 18.66; N, 7.90; S, 6.03.

20 Found: C, 49.45; H, 5.70; Cl, 18.63; N, 7.72; S, 6.04.

[Example A-56] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(E)-3-(pyridin-3-yl)propenoyl]piperazine hydrochloride

In the same manner as in Example A-4, the title compound was obtained using (E)-3-(3-pyridyl)acrylic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials.

¹H-NMR (DMSO-d₆) δ: 3.03(4H,m), 3.69(2H,br), 3.85(2H,br),
 7.51(2H,s), 7.70(1H,dd,J=8.8,2.0Hz),
 7.83(1H,dd,J=8.8,2.0Hz), 7.89(1H,dd,J=7.8,5.4Hz),
 8.16(1H,d,J=8.8Hz), 8.22(1H,d,J=2.0Hz), 8.26(1H,d,J=8.8Hz),
 5 8.51(1H,s), 8.67(1H,d,J=7.8Hz), 8.77(1H,d,J=5.4Hz),
 9.13(1H,s).

MS (FAB) m/z: 442 [(M+H)⁺, Cl³⁵], 444 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₂₀ClN₃O₃S·HCl·1/4H₂O

Calculated: C, 54.72; H, 4.49; N, 8.70; Cl, 14.68; S, 6.64.

10 Found: C, 54.81; H, 4.43; N, 8.54; Cl, 14.68; S, 6.74.

[Example A-57] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
 [(E)-3-(pyridin-4-yl)propenoyl]piperazine hydrochloride

In the same manner as in Example A-4, the title
 compound was obtained using (E)-3-(4-pyridyl)acrylic acid
 15 and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine
 hydrochloride as starting materials.

¹H-NMR (DMSO-d₆) δ: 3.03(4H,m), 3.68(2H,br), 3.82(2H,br),
 5.76(1H,s), 7.48(1H,d,J=15.1Hz), 7.65(1H,d,J=15.1Hz),
 7.72(1H,dd,J=8.8,2.0Hz), 7.83(1H,dd,J=8.8,2.0Hz),
 20 8.11(2H,br s), 8.16(1H,d,J=8.8Hz), 8.24(1H,s),
 8.27(1H,d,J=8.8Hz), 8.52(1H,s), 8.82(2H,d,J=5.9Hz).

MS (FAB) m/z: 442 [(M+H)⁺, Cl³⁵], 444 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₂₀ClN₃O₃S·HCl·1/5H₂O

Calculated: C, 54.82; H, 4.48; Cl, 14.71; N, 8.72; S, 6.65.

25 Found: C, 54.77; H, 4.41; Cl, 14.71; N, 8.50; S, 6.77.

[Example A-58] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(pyridin-4-yl)acetyl]piperazine hydrochloride

In the same manner as in Example A-4, the title compound was obtained using 4-pyridylacetic acid

5 hydrochloride and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials.

¹H-NMR (DMSO-d₆) δ: 2.99(2H,br), 3.04(2H,br), 3.57(2H,br),
3.62(2H,br), 4.00(2H,s), 7.71(2H,d,J=5.9Hz),
7.74(1H,dd,J=8.8,3.0Hz), 7.83(1H,dd,J=8.8,2.0Hz),
10 8.18(1H,d,J=8.8Hz), 8.27(1H,s), 8.29(1H,d,J=8.8Hz),
8.53(1H,s), 8.72(2H,d,J=5.9Hz).

MS (FAB) m/z: 430 [(M+H)⁺, Cl³⁵], 432 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₁H₂₀ClN₃O₃S·HCl·0.3H₂O

Calculated: C, 53.46; H, 4.61; Cl, 15.03; N, 8.91; S, 6.80.

15 Found: C, 53.28; H, 4.49; Cl, 15.18; N, 8.91; S, 6.75.

[Example A-59] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-[(3RS)-pyrrolidin-3-yl]benzoyl]piperazine hydrochloride

In the same manner as in Example A-7, the title compound was obtained using 1-[4-[(3RS)-1-tert-butoxycarbonylpyrrolidin-3-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

¹H-NMR (DMSO-d₆) δ: 1.85-1.95(1H,m), 2.30-2.40(1H,m), 3.00-3.90(13H,m), 7.72(1H,dd,J=8.6,2.2Hz),

25 7.80(1H,dd,J=8.8,2.0Hz), 7.29(2H,d,J=8.3Hz),

7.35 (2H, d, J=8.3Hz), 8.18 (1H, d, J=8.8Hz), 8.25-8.30 (2H, m),
8.49 (1H, s).

MS (FAB) m/z: 484 [(M+H)⁺, Cl³⁵], 486 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₅H₂₆ClN₃O₃S·HCl·3/2H₂O

5 Calculated: C, 54.84; H, 5.52; N, 7.67; Cl, 12.95; S, 5.86.

Found: C, 55.00; H, 5.53; N, 7.48; Cl, 13.23; S, 5.97.

[Example A-60] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
[[(1RS)-4-(pyridin-4-yl)-3-cyclohexene]carbonyl]piperazine
hydrochloride

10 In the same manner as in Example A-4, a reaction was
conducted using (1RS)-4-(4-pyridyl)-3-cyclohexenecarboxylic
acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine
hydrochloride as starting materials, whereby the title
compound was obtained.

15 ¹H-NMR (DMSO-d₆) δ: 1.50-1.60 (1H, m), 1.80-1.90 (1H, m), 2.25-
2.58 (5H, m), 2.80-2.90 (1H, m), 2.91-3.10 (1H, m), 3.46-
3.72 (4H, m), 6.94 (1H, br s), 7.71 (1H, dd, J=8.8, 2.0Hz),
7.82 (1H, dd, J=8.8, 2.0Hz), 7.96 (2H, d, J=6.8Hz),
8.15 (1H, J=8.8Hz), 8.24 (1H, J=2.0Hz), 8.27 (1H, J=8.8Hz),
20 8.50 (1H, s), 8.76 (2H, d, J=6.8Hz).

MS (FAB) m/z: 496 [(M+H)⁺, Cl³⁵], 498 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₂₆ClN₃O₃S·HCl·1.3H₂O

Calculated: C, 56.18; H, 5.37; Cl, 12.75; N, 7.56; S, 5.77.

Found: C, 56.03; H, 5.29; Cl, 12.67; N, 7.41; S, 5.77.

25 [Example A-61] 1-[(E)-4-Chlorostyrylsulfonyl]-4-[[(1RS)-4-
(pyridin-4-yl)-3-cyclohexene]carbonyl]piperazine

hydrochloride

In the same manner as in Example A-4, a reaction was conducted using (1RS)-4-(4-pyridyl)-3-cyclohexenecarboxylic acid and 1-[(E)-4-chlorostyrylsulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.59-1.70(1H,m), 1.90-1.98(1H,m), 2.31-2.56(4H,m), 2.90-3.00(1H,m), 3.13(4H,br s), 3.50-3.63(4H,m), 6.98(1H,br s), 7.35(1H,d,J=15.6Hz), 7.44(1H,d,J=15.6Hz), 7.51(2H,d,J=8.3Hz), 7.80(1H,J=8.3Hz), 7.97(1H,J=6.8Hz), 8.77(1H,J=6.8Hz).

MS (FAB) m/z: 472 [(M+H)⁺, Cl³⁵], 474 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₆ClN₃O₃S·0.9HCl·2.3H₂O

Calculated: C, 52.77; H, 5.81; Cl, 12.33; N, 7.69; S, 5.87.

Found: C, 52.61; H, 5.80; Cl, 12.54; N, 7.44; S, 6.05.

[Example A-62] cis, trans-1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[4-(pyridin-4-yl)cyclohexane]carbonyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was conducted using cis, trans-4-(4-pyridyl)cyclohexanecarboxylic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

MS (FAB) m/z: 498 [(M+H)⁺, Cl³⁵], 500 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₂₈ClN₃O₃S·1.3HCl·2H₂O

Calculated: C, 53.71; H, 5.77; Cl, 14.02; N, 7.23; S, 5.51.

Found: C, 53.70; H, 5.70; Cl, 14.21; N, 7.13; S, 5.72.

[Example A-63] cis, trans-1-[(E)-4-Chlorostyrylsulfonyl]-
4-[[4-(pyridin-4-yl)cyclohexane]carbonyl]piperazine
5 hydrochloride

In the same manner as in Example A-4, a reaction was
conducted using cis, trans-4-(4-
pyridyl)cyclohexanecarboxylic acid and 1-[(E)-4-
chlorostyrylsulfonyl]piperazine hydrochloride as starting
10 materials, whereby the title compound was obtained.

MS (FAB) m/z: 474 [(M+H)⁺, Cl³⁵], 476 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₈ClN₃O₃S·1.2HCl·0.8H₂O

Calculated: C, 54.17; H, 5.83; Cl, 14.66; N, 7.80; S, 6.03.

Found: C, 54.21; H, 6.20; Cl, 15.03; N, 7.51; S, 6.18.

15 [Example A-64] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(1,2,3,6-tetrahydropyridin-4-yl)benzoyl]piperazine
hydrochloride

In the same manner as in Example A-7, the title
compound was obtained using 1-4-(1-tert-butoxycarbonyl-
20 1,2,3,6-tetrahydropyridin-4-yl)benzoyl]-4-[(6-
chloronaphthalen-2-yl)sulfonyl]piperazine as a starting
material.

¹H-NMR (DMSO-d₆) δ: 2.67(2H, br s), 3.05(4H, br), 3.30(2H, br
s), 3.35-3.78(6H, m), 6.24(1H, br s), 7.32(2H, d, J=8.3Hz),
25 7.47(2H, d, J=8.3Hz), 7.71(1H, dd, J=8.8, 2.0Hz),
7.81(1H, dd, J=8.8, 2.0Hz), 8.17(1H, d, J=8.8Hz), 8.22-

8.28 (2H, m), 8.49 (1H, s), 9.25 (2H, br s).

MS (FAB) m/z: 496 [(M+H)⁺, Cl³⁵], 498 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₂₆ClN₃O₃S·HCl·2/5H₂O

Calculated: C, 57.86; H, 5.19; Cl, 13.14; N, 7.79; S, 5.94.

5 Found: C, 57.91; H, 5.19; Cl, 12.91; N, 7.75; S, 5.78.

[Example A-65] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(piperidin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-7, the title compound was obtained using 1-[4-(1-tert-
10 butoxycarbonylpiperidin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

¹H-NMR (DMSO-d₆) δ: 1.78-1.94 (4H, m), 2.80-3.21 (7H, m), 3.30-
3.84 (6H, m), 7.23 (2H, d, J=8.3 Hz), 7.28 (2H, d, J=8.3 Hz),
15 7.71 (1H, dd, J=8.8, 2.0 Hz), 7.80 (1H, dd, J=8.8, 2.0 Hz),
8.17 (1H, d, J=8.8 Hz), 8.22-8.27 (2H, m), 8.49 (1H, s), 8.78-
9.00 (2H, m).

MS (FAB) m/z: 498 [(M+H)⁺, Cl³⁵], 500 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₂₈ClN₃O₃S·HCl·3/5H₂O

20 Calculated: C, 57.27; H, 5.58; Cl, 13.00; N, 7.71; S, 5.88.

Found: C, 57.23; H, 5.52; Cl, 12.90; N, 7.60; S, 5.83.

[Example A-66] (3RS)-3-[(6-Chloronaphthalen-2-yl)sulfonamido]-1-[4-(pyridin-4-yl)benzoyl]pyrrolidine hydrochloride

25 In saturated solution of hydrochloride in ethanol,
(3RS)-1-tert-butoxycarbonyl-3-[(6-chloronaphthalen-2-

yl)sulfonamido]pyrrolidine was dissolved, followed by stirring at room temperature for 8 hours. The solvent was then distilled off under reduced pressure. In the same manner as in Example A-4, a reaction was conducted using the resulting residue and 4-(4-pyridyl)benzoic acid as starting materials, whereby the title compound was obtained.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.70-2.10 (2H,m), 3.00-3.65 (4H,m), 3.75-3.90 (1H,m), 7.50-8.40 (13H,m), 8.95-9.05 (2H,m).

MS (FAB) m/z : 492 $[(M+H)^+, \text{Cl}^{35}]$, 494 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{26}\text{H}_{22}\text{ClN}_3\text{O}_3\text{S}\cdot\text{HCl}\cdot 1.8\text{H}_2\text{O}$

Calculated: C, 55.68; H, 4.78; N, 7.49; Cl, 12.64; S, 5.72.

Found: C, 55.62; H, 4.94; N, 7.67; Cl, 12.76; S, 5.79.

[Example A-67] (3RS)-1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[4-(pyridin-4-yl)benzamido]pyrrolidine hydrochloride

In saturated solution of hydrochloride in ethanol, (3RS)-1-tert-butoxycarbonyl-3-[4-(4-pyridyl)benzamido]pyrrolidine was dissolved, followed by stirring at room temperature for 4 hours. The solvent was then distilled off under reduced pressure. In the same manner as in Example A-1, a reaction was conducted using the resulting residue and 6-chloro-2-naphthylsulfonyl chloride as starting materials, whereby the title compound was obtained as a hydrochloride.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.90-2.10 (2H,m), 3.00-3.60 (4H,m), 4.15-

4.25 (1H, m), 7.57 (1H, dd, J=8.8, 2.0 Hz), 7.73 (2H, d, J=8.8 Hz),
 7.85 (1H, dd, J=8.8, 2.0 Hz), 7.90 (2H, d, J=8.8 Hz), 7.95-
 8.05 (2H, m), 8.18 (1H, d, J=8.8 Hz), 8.30-8.40 (3H, m),
 8.50 (1H, s), 8.98 (2H, d, J=6.4 Hz).

5 MS (FAB) m/z: 492 [(M+H)⁺, Cl³⁵], 494 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₂₂ClN₃O₃S·0.8HCl·0.8H₂O

Calculated: C, 58.31; H, 4.59; N, 7.85; Cl, 11.92; S, 5.99.

Found: C, 58.27; H, 4.68; N, 7.80; Cl, 11.94; S, 6.04.

[Example A-68] 1-[[(E)-2-(6-Chloropyridin-3-

10 yl)ethylene]sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

To a suspension of 1-tert-butoxycarbonyl-4-[[(E)-2-(6-chloropyridin-3-yl)ethylene]sulfonyl]piperazine (390 mg) in ethanol (2 ml), saturated hydrochloric acid - ethanol (6 ml) was added, followed by stirring for 3 hours. The
 15 reaction mixture was concentrated and the residue was dissolved in N,N-dimethylformamide (10 ml). To the resulting solution, 4-(4-pyridyl)benzoic acid hydrochloride (262 mg) and N-methylmorpholine (1.00 ml) were added. Under ice cooling, 1H-benzotriazol-1-

20 yloxytripyrrolidinophosphonium hexafluorophosphate was

added, followed by stirring at room temperature for 4 hours. The reaction mixture was diluted with ethyl

acetate, washed successively with water, a saturated

aqueous solution of sodium bicarbonate and saturated

25 aqueous NaCl solution and then dried over anhydrous sodium

sulfate. The residue obtained by distilling off the

solvent under reduced pressure was recrystallized from a mixed solvent of dichloromethane and ethyl acetate. The resulting crystals were suspended in ethanol. Saturated hydrochloric acid - ethanol (6 ml) was added to the
 5 resulting suspension, followed by concentration into its hydrochloride. The resulting solid was recrystallized from ethanol, whereby the title compound (245 mg, 47%) was obtained as a colorless solid.

¹H-NMR (DMSO-d₆) δ: 3.10-3.31(4H,br), 3.40-3.84(4H,br),
 10 7.50(1H,d,J=15.9Hz), 7.52(1H,d,J=15.9Hz),
 7.46(3H,d,J=8.3Hz), 8.06(2H,d,J=8.3Hz), 8.28-8.33(3H,m),
 8.79(1H,d,J=2.0Hz), 8.94(2H,d,J=6.4Hz).

MS (FAB) m/z: 469 [(M+H)⁺, Cl³⁵], 471 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₃H₂₁ClN₄O₃S·HCl·0.4H₂O

15 Calculated: C, 53.89; H, 4.48; N, 10.93; Cl, 13.83; S,
 6.26.

Found: C, 53.95; H, 4.47; N, 11.02; Cl, 13.91; S,
 6.39.

[Example A-69] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[2-
 20 methyl-4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Referential Example 7, a reaction was conducted using 1-(4-bromo-2-methylbenzoyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material, whereby the title compound was obtained.

25 ¹H-NMR (DMSO-d₆) δ: 2.20(3H,s), 2.80-4.00(8H,m),

7.36 (1H, d, J=8.3Hz), 7.73 (1H, dd, J=8.8, 2.4Hz), 7.75-
7.85 (2H, m), 7.88 (1H, s), 8.18 (1H, d, J=8.8Hz), 8.20-
8.30 (4H, m), 8.50 (1H, br s), 8.90 (2H, d, J=6.8Hz).

MS (FAB) m/z: 506 [(M+H)⁺, Cl³⁵], 508 [(M+H)⁺, Cl³⁷].

5 [Example A-70] 4-[4-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-3-methylphenyl]pyridine N-oxide

In the same manner as in Example A-6, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[2-
10 methyl-4-(pyridin-4-yl)benzoyl]piperazine as a starting material, whereby the title compound was obtained.

¹H-NMR (CDCl₃)δ: 2.27 (3H, s), 2.80-4.20 (8H, m),
7.16 (1H, d, J=8.3Hz), 7.38 (1H, J=8.3Hz), 7.41 (1H, br s),
7.48 (2H, d, J=6.8Hz), 7.61 (1H, dd, J=8.8, 1.5Hz),
15 7.75 (1H, d, J=8.8Hz), 7.91-7.97 (3H, m), 8.28 (2H, d, J=6.8Hz),
8.31 (1H, br s).

MS (FAB) m/z: 522 [(M+H)⁺, Cl³⁵], 524 [(M+H)⁺, Cl³⁵].

Elementary analysis for C₂₇H₂₄ClN₃O₄S·H₂O

Calculated: C, 60.05; H, 4.85; Cl, 6.56; N, 7.78; S, 5.94.

20 Found: C, 59.98; H, 4.89; Cl, 6.51; N, 7.48; S, 5.92.

[Example A-71] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-methyl-4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was conducted using 3-methyl-4-(4-pyridyl)benzoic acid
25 hydrochloride as a starting material, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.27(3H,s), 3.08(4H,br), 3.47(2H,br),
 3.72(2H,br), 7.26-7.37(3H,m), 7.73(1H,dd,J=8.8,2.0Hz),
 7.83(1H,dd,J=8.8,2.0Hz), 7.86(2H,d,J=6.8Hz),
 8.18(1H,d,J=8.8Hz), 8.25-8.29(2H,m), 8.50(1H,br s),
 8.87(2H,d,J=6.8Hz).

MS (FAB) m/z: 506 [(M+H)⁺, Cl³⁵], 508 [(M+H)⁺, Cl³⁵].

Elementary analysis for C₂₇H₂₄ClN₃O₃S·0.9HCl·1.7H₂O

Calculated: C, 56.95; H, 5.01; Cl, 11.83; N, 7.38; S, 5.63.

Found: C, 57.08; H, 5.04; Cl, 11.75; N, 7.37; S, 5.49.

[Example A-72] 4-4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-piperazin-1-yl]carbonyl]-2-methylphenyl]pyridine N-oxide

In the same manner as in Example A-6, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[3-methyl-4-(pyridin-4-yl)benzoyl piperazine as a starting material, whereby the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.28(3H,s), 3.13(4H,br), 3.63(2H,br),
 3.86(2H,br), 7.15-7.28(5H,m), 7.60(1H,d,J=8.8Hz),
 7.76(1H,d,J=8.8Hz), 7.90-7.96(3H,m), 8.26(2H,d,J=6.8Hz),
 8.31(1H,s).

MS (FAB) m/z: 522 [(M+H)⁺, Cl³⁵], 524 [(M+H)⁺, Cl³⁵].

Elementary analysis for C₂₇H₂₄ClN₃O₄S·H₂O

Calculated: C, 60.05; H, 4.85; Cl, 6.56; N, 7.78; S, 5.94.

Found: C, 59.71; H, 4.68; Cl, 6.87; N, 7.63; S, 5.91.

[Example A-73] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-

(2-methylpyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was conducted using 4-(2-methyl-4-pyridyl)benzoic acid hydrochloride as a starting material, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.76(3H,s), 3.00-3.90(8H,m),
7.56(2H,d,J=8.3Hz), 7.74(1H,dd,J=8.8,2.4Hz),
7.38(1H,dd,J=8.8,2.0Hz), 8.00(2H,d,J=8.3Hz),
8.14(1H,d,J=6.4Hz), 8.19(1H,d,J=8.8Hz), 8.22-8.29(3H,m),
8.51(1H,br s), 8.80(1H,d,J=6.4Hz).

MS (FAB) m/z: 506 [(M+H)⁺, Cl³⁵], 508 [(M+H)⁺, Cl³⁵].

Elementary analysis for C₂₇H₂₄ClN₃O₃S·HCl·2H₂O

Calculated: C, 56.06; H, 5.05; Cl, 12.26; N, 7.26; S, 5.54.

Found: C, 55.84; H, 5.03; Cl, 12.26; N, 6.87; S, 5.54.

[Example A-74] 4-4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-piperazin-1-yl]carbonyl]phenyl]-2-methylpyridine N-oxide

In the same manner as in Example A-6, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(2-methylpyridin-4-yl)benzoyl]piperazine as a starting material, whereby the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.58(3H,s), 3.13(4H,br), 3.65(2H,br),
3.84(2H,br), 7.34(1H,dd,J=6.8,2.4Hz), 7.41(2H,d,J=8.3Hz),
7.45(1H,d,J=2.4Hz), 7.56-7.62(3H,m),
7.76(1H,dd,J=8.8,2.0Hz), 7.91-7.96(3H,m), 8.28-8.32(2H,m).

MS (FAB) m/z: 522 [(M+H)⁺, Cl³⁵], 524 [(M+H)⁺, Cl³⁵].

Elementary analysis for C₂₇H₂₄ClN₃O₄S·H₂O·0.05CH₂Cl₂

Calculated: C, 59.69; H, 4.83; Cl, 7.16; N, 7.72; S, 5.89.

Found: C, 59.47; H, 4.87; Cl, 6.98; N, 7.48; S, 6.10.

5 [Example A-75] 4-4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[2-(morpholin-4-yl)ethylamino]carbonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-4, a reaction was
10 conducted using 4-[4-[[2-carboxy-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide and 4-(2-aminoethyl)morpholine as starting materials, whereby the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.22(4H,s), 2.35-2.80(6H,br), 3.20-
15 3.90(3H,br), 3.74(4H,s), 4.20-4.60(1H,br), 5.25-5.50(1H,br), 6.80-7.20(1H,br), 7.45-7.70(7H,m), 7.76(1H,d,J=8.8Hz), 7.85-7.95(3H,m), 8.26(2H,d,J=6.9Hz), 8.32(1H,s).

MS (FAB) m/z: 664 [(M+H)⁺, Cl³⁵], 666 [(M+H)⁺, Cl³⁷].

20 [Example A-76] 4-4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(dimethylamino)ethylamino]carbonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-4, a reaction was
25 conducted using 4-[4-[[2-carboxy-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

and 2-(dimethylamino)ethylamine as starting materials,
whereby the title compound was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.29(6H,s), 2.35-2.75(6H,br), 3.35-
3.90(3H,br), 4.40-4.60(1H,br), 5.25-5.50(1H,br), 7.00-
7.20(1H,br), 7.45-7.65(7H,m), 7.77(1H,dd, $J=8.8, 1.4\text{Hz}$),
7.85-7.95(3H,m), 8.26(2H,d, $J=7.3\text{Hz}$), 8.34(1H,s).

MS (FAB) m/z : 622 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 624 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$.

Elementary analysis for $\text{C}_{31}\text{H}_{32}\text{N}_5\text{O}_5\text{S}\cdot 0.05\text{CH}_2\text{Cl}_2\cdot 2\text{H}_2\text{O}$

Calculated: C, 56.30; H, 5.49; N, 10.57; Cl, 5.89; S, 4.84.

Found: C, 56.27; H, 5.37; N, 10.39; Cl, 6.01; S, 4.91.

[Example A-77] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-
methoxycarbonylmethyl-1-[4-(pyridin-2-yl)benzoyl]piperazine

In the same manner as in Example A-68, a reaction was
conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-
methoxycarbonylmethylpiperazine (723 mg) and 4-(2-
pyridyl)benzoic acid hydrochloride as starting materials,
whereby the title compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.30-4.50(11H,m), 5.06(1H,br s), 7.30-
7.50(3H,m), 7.72(1H,dd, $J=8.8, 2.0\text{Hz}$), 7.80-7.85(1H,m), 7.85-
7.95(1H,m), 7.98(1H,d, $J=7.8\text{Hz}$), 8.10(2H,d, $J=8.3\text{Hz}$),
8.18(1H,d, $J=8.8\text{Hz}$), 8.25-8.30(2H,m), 8.51(1H,s), 8.65-
8.70(1H,m).

MS (FAB) m/z : 564 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 566 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$.

Elementary analysis for $\text{C}_{29}\text{H}_{26}\text{ClN}_3\text{O}_5\text{S}\cdot 1.1\text{H}_2\text{O}$

Calculated: C, 59.66; H, 4.87; N, 7.20; Cl, 6.07; S, 5.49.

Found: C, 59.53; H, 4.61; N, 7.05; Cl, 6.33; S, 5.70.

[Example A-78] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-carboxymethyl-1-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride

5 In the same manner as in Example A-3, a reaction was conducted using 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-methoxycarbonylmethyl-1-[4-(pyridin-2-yl)benzoyl]piperazine as a starting material, whereby the title compound was obtained.

10 $^1\text{H-NMR}$ (DMSO- d_6) δ : 2.30-4.50 (8H, m), 5.05 (1H, br s), 7.35-7.40 (1H, m), 7.43 (2H, d, $J=8.8\text{Hz}$), 7.72 (1H, d, $J=8.3\text{Hz}$), 7.81 (1H, d, $J=8.8\text{Hz}$), 7.85-7.90 (1H, m), 7.97 (1H, d, $J=7.8\text{Hz}$), 8.08 (2H, d, $J=8.8\text{Hz}$), 8.17 (1H, d, $J=8.8\text{Hz}$), 8.25-8.30 (2H, m), 8.49 (1H, s), 8.65-8.70 (1H, m).

15 MS (FAB) m/z : 550 $[(M+H)^+, \text{Cl}^{35}]$, 552 $[(M+H)^+, \text{Cl}^{35}]$.

Elementary analysis for $\text{C}_{28}\text{H}_{24}\text{ClN}_3\text{O}_5\text{S} \cdot 0.4\text{HCl} \cdot 0.9\text{H}_2\text{O}$

Calculated: C, 57.90; H, 4.55; N, 7.23; Cl, 8.55; S, 5.52.

Found: C, 57.76; H, 4.26; N, 7.02; Cl, 8.44; S, 5.27.

[Example A-79] 2-Carbamoylmethyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride

20

In the same manner as in Example A-35, a reaction was conducted using 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-carboxymethyl-1-[4-(pyridin-2-yl)benzoyl]piperazine as a starting material, whereby the title compound was obtained.

25

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.20-4.50 (8H, m), 5.10 (1H, br s),

6.96(2H,br s), 7.45-7.55(3H,m), 7.70-7.85(3H,m), 8.05-8.35(6H,m), 8.50(1H,s), 8.81(1H,d,J=4.9Hz).

MS (FAB) m/z: 549 [(M+H)⁺, Cl³⁵], 551 [(M+H)⁺, Cl³⁵].

Elementary analysis for C₂₈H₂₅ClN₄O₄S·1.3HCl·1.5H₂O

5 Calculated: C, 53.94; H, 4.74; N, 8.99; Cl, 13.08; S, 5.14.

Found: C, 53.85; H, 4.87; N, 8.80; Cl, 13.19; S, 5.27.

[Example A-80] 1-[(Z)-4-Chloro-β-(2-hydroxyethan-1-yl)-β-styrylsulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride

10 Under ice cooling, 4-tert-butoxycarbonyl-1-[(Z)-4-chloro-β-[2-(methoxymethoxy)ethyl]-β-styrylsulfonyl]piperazine (355 mg) was dissolved in ethanol (3 ml), followed by the addition of saturated solution of hydrochloride (6 ml) in ethanol. The resulting mixture was stirred at room temperature for 1 hour. After the reaction mixture was concentrated under reduced pressure, a reaction was effected in the same manner as in Example A-4 by using the resulting residue, whereby the title compound (285 mg, 65%) was obtained.

20 ¹H-NMR (DMSO-d₆) δ: 2.58(2H,t,J=6.6Hz), 3.06(4H,br s), 3.15-3.60(4H,br), 3.68(2H,t,J=6.6Hz), 7.24(1H,s), 7.38(2H,d,J=8.6Hz), 7.40(2H,d,J=8.6Hz), 7.47-7.57(3H,m), 8.02-8.10(2H,m), 8.14(2H,d,J=8.3Hz), 8.74(1H,d,J=4.4Hz). MS (FAB) m/z: 512 (M+H)⁺.

25 [Example A-81] 1-[(E)-4-Chloro-β-(2-hydroxyethan-1-yl)-β-

styrylsulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine
hydrochloride

In the same manner as in Example A-80, the title
compound (240 mg, 74%) was obtained using 4-tert-

5 butoxycarbonyl-1-[(E)-4-chloro- β -(2-
(methoxymethoxy)ethyl)- β -styrylsulfonyl]piperazine (355
mg) as a starting material.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.74 (2H, t, $J=7.3\text{Hz}$), 3.27 (4H, br s),
3.37-3.85 (6H, m), 7.45 (1H, s), 7.50-7.60 (5H, m),
10 7.68 (2H, d, $J=8.3\text{Hz}$), 8.06-8.17 (4H, m), 8.75 (1H, d, $J=4.9\text{Hz}$).

MS (FAB) m/z : 512 ($M+H$) $^+$.

Elementary analysis for $\text{C}_{26}\text{H}_{26}\text{ClN}_3\text{O}_4\text{S}\cdot 1.1\text{HCl}\cdot 0.8\text{H}_2\text{O}$

Calculated: C, 55.12; H, 5.11; N, 7.42; Cl, 13.14; S, 5.66.

Found: C, 55.22; H, 5.21; N, 7.20; Cl, 12.97; S, 5.66.

15 In the same manner as in Example A-7 or Example A-1,
the compounds shown in Examples A-82 to A-86 were
synthesized.

[Example A-82] 1-[(6-Chloro-1-phenylsulfonylindol-2-
y)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

20 $^1\text{H-NMR}$ (CDCl_3) δ : 2.80-4.30 (8H, br), 7.34 (1H, d, $J=8.5, 1.7\text{Hz}$),
7.43-7.62 (9H, m), 7.69 (2H, d, $J=7.8\text{Hz}$), 8.04 (2H, d, $J=7.8\text{Hz}$),
8.33 (1H, s), 8.70 (2H, br s).

Elementary analysis for $\text{C}_{30}\text{H}_{25}\text{ClN}_4\text{O}_5\text{S}_2$

Calculated: C, 58.01; H, 4.06; Cl, 5.71; N, 9.02; S, 10.32.

25 Found: C, 58.34; H, 4.23; Cl, 5.78; N, 8.85; S, 9.96.

[Example A-83] 1-[(5-Chloro-3-methylbenzo[b]thien-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

¹H-NMR (DMSO-d₆) δ: 2.67(3H,s), 3.15-3.31(4H,br), 3.37-3.84(4H,br), 7.58(1H,m), 7.65(1H,dd,J=8.8,2.0Hz), 7.92-8.03(2H,br), 8.13(1H,d,J=2.0Hz), 8.15-8.24(4H,m), 8.79-8.92(2H,br).

MS (FAB) m/z: 512 [(M+H)⁺, Cl³⁵], 514 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₅H₂₂ClN₃O₃S₂ · HCl · 0.3H₂O

Calculated: C, 54.21; H, 4.29; Cl, 12.80; N, 7.59; S, 11.58.

Found: C, 54.25; H, 4.25; Cl, 12.98; N, 7.52; S, 11.52.

[Example A-84] 1-[(1-Phenylsulfonyl-5-trimethylsilylethynylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

¹H-NMR (CDCl₃) δ: 0.25(9H,s), 3.35-4.00(8H,m), 7.43(2H,t,J=8.1Hz), 7.47-7.64(7H,m), 7.64-7.74(3H,m), 8.00(2H,d,J=8.1Hz), 8.23(1H,d,J=8.8Hz), 8.71(2H,br s).

[Example A-85] 1-[(5-Chlorobenzo[b]furan-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

¹H-NMR (DMSO-d₆) δ: 3.20-3.55(6H,br), 3.60-3.90(2H,br), 7.61(1H,dd,J=8.8,2.0Hz), 7.61(2H,d,J=8.8Hz), 7.68(1H,s), 7.84(1H,d,J=8.8Hz), 7.94(1H,d,J=2.0Hz), 8.05(2H,d,J=8.8Hz), 8.34(2H,d,J=5.9Hz), 8.95(2H,d,J=5.9Hz).

MS (FAB) m/z: 482 [(M+H)⁺, Cl³⁵], 484 [(M+H)⁺, Cl³⁷].

Elementary analysis for $C_{24}H_{20}ClN_3O_4S \cdot HCl \cdot 0.6H_2O$

Calculated: C, 54.47; H, 4.23; Cl, 13.40; N, 7.94; S, 6.06.

Found: C, 54.48; H, 4.14; Cl, 13.41; N, 7.83; S, 6.17.

[Example A-86] 1-[(6-Chlorobenzo[b]furan-2-yl)sulfonyl]-4-
5 [4-(pyridin-4-yl)benzoyl]piperazine

1H -NMR (DMSO- d_6) δ : 3.20-3.45 (4H, br), 3.35-3.55 (2H, br),
3.65-3.85 (2H, br), 7.48 (1H, d, $J=8.8$ Hz), 7.59 (2H, d, $J=7.8$ Hz),
7.73 (1H, s), 7.80-8.10 (1H, m), 7.86 (1H, d, $J=8.8$ Hz),
7.98 (1H, s), 8.04 (2H, d, $J=7.8$ Hz), 8.20-8.32 (1/2H, m), 8.60-
10 9.49 (1H, br), 8.90-8.93 (1/2H, m).

MS (FAB) m/z : 482 $[(M+H)^+, Cl^{35}]$, 484 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{24}H_{20}ClN_3O_4S \cdot HCl \cdot 0.3H_2O$

Calculated: C, 55.03; H, 4.16; Cl, 13.54; N, 8.02; S, 6.12.

Found: C, 55.06; H, 4.12; Cl, 13.62; N, 7.89; S, 6.11.

15 In the same manner as in Example A-7 or Example A-4,
the compounds shown in Examples A-87 to A-93 were
synthesized.

[Example A-87] 1-[(5-Chloro-1-phenylsulfonylindol-2-
yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

20 1H -NMR ($CDCl_3$) δ : 3.45-3.53 (4H, br), 3.53-3.98 (4H, br), 7.40-
7.50 (4H, m), 7.52-7.60 (6H, m), 7.70 (2H, d, $J=8.3$ Hz),
8.01 (2H, d, $J=8.3$ Hz), 8.24 (1H, d, $J=9.3$ Hz), 8.73 (2H, br).

MS (FAB) m/z : 621 $[(M+H)^+, Cl^{35}]$, 623 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{30}H_{25}ClN_4O_5S_2 \cdot 0.1CH_2Cl_2$

25 Calculated: C, 57.42; H, 4.03; Cl, 6.76; N, 8.90; S, 10.19.

Found: C, 57.10; H, 4.35; Cl, 6.58; N, 8.80; S, 10.04.

[Example A-88] 1-[(1-Phenylsulfonyl-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

¹H-NMR (CDCl₃) δ: 3.43-3.53(4H,br), 3.53-3.94(4H,br),
 5 7.43(1H,t,J=7.6Hz), 7.40-7.46(2H,m), 7.48-7.65(10H,m),
 7.69(2H,d,J=8.3Hz), 8.04(3H,m), 8.30(1H,d,J=8.3Hz),
 8.69(2H,m).

MS (FAB) m/z: 587 (M+H)⁺

Elementary analysis for C₃₀H₂₆N₄O₅S₂·0.5H₂O

10 Calculated: C, 60.49; H, 4.57; N, 9.41; S, 10.77.

Found: C, 60.32; H, 4.73; N, 9.41; S, 10.43.

[Example A-89] 1-[(1-Phenylsulfonyl-5-chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]homopiperazine

¹H-NMR (CDCl₃) δ: 1.85-1.92(1H,m), 2.13-2.20(1H,m), 3.47-
 15 3.76(1H,m), 3.54-3.73(5H,m), 3.87-3.98(2H,m), 7.38-
 7.60(11H,m), 7.69(2H,d,J=6.8Hz), 8.02-8.08(2H,m), 8.18-
 8.23(1H,m), 8.69(2H,d,J=5.9Hz).

MS (FAB) m/z: 635 [(M+H)⁺, Cl³⁵], 637 [(M+H)⁺, Cl³⁷].

[Example A-90] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride
 20

¹H-NMR (DMSO-d₆) δ: 2.92-3.26(4H,br), 3.35-3.78(4H,br),
 7.03(1H,d,J=2.0Hz), 7.34(1H,dd,J=8.8,2.4Hz), 7.47-
 7.56(4H,m), 7.80(1H,d,J=2.0Hz), 8.02-8.16(4H,m),
 8.73(1H,d,J=4.9Hz), 12.40(1H,s).

25 MS (FAB) m/z: 481 [(M+H)⁺, Cl³⁵], 483 [(M+H)⁺, Cl³⁷].

Elementary analysis for $C_{24}H_{21}ClN_4O_3S \cdot 0.9HCl \cdot 1.6H_2O$

Calculated: C, 53.13; H, 4.66; Cl, 12.41; N, 10.33; S, 5.91.

Found: C, 53.29; H, 4.89; Cl, 12.40; N, 10.15; S, 5.92.

[Example A-91] 1-[(5-Chloro-1-methylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

1H -NMR ($CDCl_3$) δ : 3.09-3.45(4H,br), 3.49-4.03(4H,br), 3.70(3H,s), 7.08(1H,m), 7.33(1H,d,J=8.8Hz), 7.37(2H,d,J=7.8Hz), 7.44-7.53(3H,m), 7.64-7.69(3H,m), 8.69(2H,br).

MS (FAB) m/z: 495 $[(M+H)^+, Cl^{35}]$, 497 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{25}H_{23}ClN_4O_3S \cdot 0.1HCl \cdot 0.2H_2O$

Calculated: C, 56.12; H, 4.60; Cl, 13.25; N, 10.47; S, 5.99.

Found: C, 56.13; H, 4.54; Cl, 13.25; N, 10.40; S, 5.99.

[Example A-92] 1-[(5-Chloro-1-ethylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

1H -NMR ($DMSO-d_6$) δ : 1.30(3H,t,J=6.8Hz), 3.15-3.37(4H,br), 3.38-3.57(2H,br), 3.65-3.87(2H,br), 4.47(2H,q,J=6.8Hz), 7.17(1H,s), 7.41(1H,dd,J=8.8,2.0Hz), 7.63(2H,d,J=8.3Hz), 7.73(1H,d,J=8.8Hz), 7.81(1H,d,J=2.0Hz), 8.05(2H,d,J=8.3Hz), 8.31(2H,d,J=6.4Hz), 8.94(2H,d,J=6.4Hz).

MS (FAB) m/z: 509 $[(M+H)^+, Cl^{35}]$, 511 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{26}H_{25}ClN_4O_3S \cdot 1.1HCl \cdot 1.2H_2O$

Calculated: C, 54.71; H, 5.03; Cl, 13.04; N, 9.82; S, 5.62.

Found: C, 54.51; H, 5.11; Cl, 13.06; N, 9.68; S, 5.71.

[Example A-93] 1-[(5-Chloro-1-ethoxycarbonylmethylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

1H -NMR (DMSO- d_6) δ : 1.19(3H,t,J=6.8Hz), 3.00-3.29(4H,br),
3.30-3.85(4H,br), 4.14(2H,q,J=6.8Hz), 5.30(2H,s), 7.17-
7.27(1H,m), 7.42(1H,d,J=8.8Hz), 7.59(2H,d,J=7.8Hz),
7.73(1H,d,J=8.8Hz), 7.84(1H,s), 8.01(2H,d,J=7.8Hz),
8.21(2H,d,J=6.3Hz), 8.88(2H,d,J=6.3Hz).

MS (FAB) m/z: 567 [(M+H) $^+$, Cl 35], 569 [(M+H) $^+$, Cl 37].

Elementary analysis for $C_{28}H_{27}ClN_4O_5S \cdot 0.9HCl \cdot 0.5H_2O$

Calculated: C, 55.23; H, 4.78; Cl, 11.06; N, 9.20; S, 5.27.

Found: C, 54.91; H, 5.06; Cl, 10.78; N, 9.22; S, 5.45.

In the same manner as in Example A-4, the compounds shown in Examples A-94 to A-98 were synthesized.

[Example A-94] 1-[(5-Chlorobenzothiazol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

1H -NMR (DMSO- d_6) δ : 3.28-3.90(8H,m), 7.61(2H,d,J=8.3Hz),
7.77(1H,dd,J=8.8,2.0Hz), 8.04(2H,d,J=8.8Hz),
8.28(2H,d,J=6.4Hz), 8.38(1H,d,J=8.8Hz), 8.43(1H,d,J=2.0Hz),
8.93(2H,d,J=6.4Hz).

MS (FAB) m/z: 499 [(M+H) $^+$, Cl 35], 501 [(M+H) $^+$, Cl 37].

Elementary analysis for $C_{23}H_{19}ClN_4O_3S_2 \cdot HCl \cdot 0.6H_2O$

Calculated: C, 50.57; H, 3.91; Cl, 12.98; N, 10.26; S,

11.74.

Found: C, 50.72; H, 3.90; Cl, 13.22; N, 9.99; S,

11.35.

[Example A-95] 1-[(6-Chlorobenzothiazol-2-yl)sulfonyl]-4-

5 [4-(pyridin-4-yl)benzoyl]piperazine

$^1\text{H-NMR}$ (DMSO- d_6) δ : 3.28-3.90 (8H, m), 7.55 (2H, d, $J=8.3\text{Hz}$),

7.77 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.85-7.93 (4H, m),

8.29 (1H, d, $J=8.8\text{Hz}$), 8.50 (1H, d, $J=2.0\text{Hz}$), 8.73 (2H, d, $J=6.4\text{Hz}$).

MS (FAB) m/z : 499 $[(M+H)^+, \text{Cl}^{35}]$, 501 $[(M+H)^+, \text{Cl}^{37}]$.

10 Elementary analysis for $\text{C}_{23}\text{H}_{19}\text{ClN}_4\text{O}_3\text{S}_2 \cdot 0.25\text{HCl} \cdot 0.5\text{H}_2\text{O}$

Calculated: C, 53.42; H, 3.95; Cl, 8.57; N, 10.83; S,

12.40.

Found: C, 53.22; H, 3.91; Cl, 8.41; N, 10.70; S,

12.59.

15 [Example A-96] 1-[(5-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-

[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

$^1\text{H-NMR}$ (DMSO- d_6) δ : 3.02-4.00 (8H, m), 7.51 (2H, d, $J=8.8\text{Hz}$),

7.62 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.71 (2H, d, $J=5.4\text{Hz}$),

7.82 (2H, d, $J=8.8\text{Hz}$), 8.04 (1H, s), 8.17 (1H, d, $J=2.0\text{Hz}$),

20 8.19 (1H, d, $J=8.8\text{Hz}$), 8.65 (2H, d, $J=5.4\text{Hz}$).

MS (FAB) m/z : 498 $[(M+H)^+, \text{Cl}^{35}]$, 499 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{24}\text{H}_{20}\text{ClN}_3\text{O}_3\text{S}_2 \cdot \text{HCl}$

Calculated: C, 53.93; H, 3.96; Cl, 13.27; N, 7.86; S,

12.00.

25 Found: C, 53.79; H, 4.07; Cl, 13.37; N, 7.70; S,

12.07.

[Example A-97] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

¹H-NMR (DMSO-d₆) δ: 3.03-3.88 (8H, m), 7.56-7.61 (3H, m),

5 8.02 (2H, d, J=8.8 Hz), 8.09 (2H, d, J=8.8 Hz), 8.29 (2H, d, J=6.3 Hz),

8.34 (1H, d, J=2.0 Hz), 8.94 (2H, d, J=6.3 Hz).

MS (FAB) m/z: 498 [(M+H)⁺, Cl³⁵], 500 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₀ClN₃O₃S₂·HCl·H₂O

Calculated: C, 52.17; H, 4.20; Cl, 12.83; N, 7.61; S,

10 11.61.

Found: C, 52.18; H, 4.14; Cl, 12.84; N, 7.56; S,

11.70.

[Example A-98] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride

15 ¹H-NMR (DMSO-d₆) δ: 3.02-3.90 (8H, m), 7.55 (2H, d, J=8.3 Hz),

7.58 (1H, dd, J=8.3, 1.5 Hz), 7.62 (1H, t, J=6.3 Hz), 8.07-

8.20 (6H, m), 8.33 (1H, d, J=1.5 Hz), 8.77 (1H, d, J=5.4 Hz).

MS (FAB) m/z: 498 [(M+H)⁺, Cl³⁵], 500 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₀ClN₃O₃S₂·HCl·0.8H₂O

20 Calculated: C, 52.52; H, 4.15; Cl, 12.92; N, 7.66; S,

11.68.

Found: C, 52.69; H, 4.18; Cl, 12.63; N, 7.46; S,

11.68.

[Example A-99] 1-[(6-Chloroindol-2-yl)sulfonyl]-4-[4-

25 (pyridin-4-yl)benzoyl]piperazine

In tetrahydrofuran (4.0 ml), 1-[(1-phenylsulfonyl-6-chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine (380 mg) was dissolved, followed by the addition of methanol (4.0 ml) and potassium hydroxide (34.3 mg) at room temperature. The resulting mixture was stirred for 2 hours. To the reaction mixture, a saturated aqueous solution (30 ml) of ammonium chloride was added to make it weakly acidic. Then, a saturated aqueous solution (40 ml) of sodium bicarbonate was added to make the resulting mixture to weakly alkaline. The resulting mixture was added with dichloromethane (30 ml). The organic layer thus separated was extracted further with dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure. The residue thus obtained was purified by preparative thin-layer chromatography on a silica gel (dichloromethane : acetone : methanol = 20:2:1), followed by recrystallization from a mixed solvent of hexane and dichloromethane, whereby the title compound (157 mg, 53%) was obtained as a white solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.70-4.20 (8H, br), 7.02 (1H, br s), 7.23 (1H, dd, $J=8.3, 1.8\text{Hz}$), 7.42-7.50 (5H, m), 7.62-7.68 (3H, m), 8.69 (2H, d, $J=5.9\text{Hz}$), 8.78 (1H, br s).

In the same manner as in Example A-99, the compounds shown in Examples A-100 to A-103 were synthesized.

[Example A-100] 1-[(Indol-2-yl)sulfonyl]-4-[4-(pyridin-4-

yl)benzoyl]piperazine

¹H-NMR (DMSO-d₆) δ: 3.00-3.20(4H,br), 3.42-3.84(4H,br),
7.05(1H,s), 7.16(1H,t,J=7.3Hz), 7.33(1H,m), 7.50(3H,m),
7.72(2H,d,J=6.3Hz), 7.82(2H,d,J=7.8Hz), 7.65(2H,d,J=4.9Hz),
12.20(1H,s).

MS (FAB) m/z: 447 (M+H)⁺

Elementary analysis for C₂₄H₂₂N₄O₃S·0.2H₂O

Calculated: C, 64.04; H, 5.02; N, 12.45; S, 7.12.

Found: C, 64.23; H, 5.30; N, 12.06; S, 7.07.

10 [Example A-101] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

¹H-NMR (DMSO-d₆) δ: 2.94-3.25(4H,br), 3.30-3.41(4H,br),
7.03(1H,s), 7.33(1H,d,J=8.8Hz), 7.52(1H,d,J=8.8Hz),
7.59(2H,d,J=7.3Hz), 7.80(1H,s), 8.03(2H,d,J=7.3Hz),
8.33(2H,d,J=5.9Hz), 8.95(2H,d,J=5.9Hz), 12.5(1H,s).

MS (FAB) m/z: 481 [(M+H)⁺, Cl³⁵], 483 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₁ClN₄O₃S·HCl·1.5H₂O

Calculated: C, 52.95; H, 4.63; Cl, 13.02; N, 10.29; S,
5.89.

20 Found: C, 53.34; H, 4.74; Cl, 12.87; N, 9.92; S, 5.77.

[Example A-102] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]homopiperazine

¹H-NMR (DMSO-d₆) δ: 1.75-1.85(1H,br), 2.02-2.13(1H,br),
3.50-3.73(6H,m), 3.92-3.96(1H,br), 7.00(1H,m), 7.28-
7.35(1H,m), 7.43-7.52(2H,m), 7.58(1H,d,J=7.8Hz), 7.74-

7.78 (1H,m), 7.93-8.07 (2H,m), 8.14-8.36 (2H,m), 8.83-8.95 (2H,m), 12.43 (1H,m).

MS (FAB) m/z: 495 [(M+H)⁺, Cl³⁵], 497 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₅H₂₃ClN₄O₃S·1.05HCl·0.85H₂O

5 Calculated: C, 54.73; H, 4.73; Cl, 13.25; N, 10.21; S, 5.85.

Found: C, 55.04; H, 5.03; Cl, 13.23; N, 9.89; S, 5.61.

[Example A-103] 1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

10 ¹H-NMR (CDCl₃) δ: 2.85-3.40 (4H,br), 3.06 (1H,s), 3.40-4.10 (4H,br), 7.01 (1H,br s), 7.39 (1H,d,J=8.8Hz), 7.45 (2H,d,J=8.3Hz), 7.45-7.50 (3H,m), 7.64 (2H,d,J=8.3Hz), 7.89 (1H,br s), 8.70 (2H,d,J=6.8Hz), 9.55 (1H,br s).

MS (FAB) m/z: 471 (M+H)⁺

15 [Example A-104] cis-4-[(5-Chloroindol-2-yl)sulfonyl]-2,6-dimethyl-1-[4-(pyridin-4-yl)benzoyl]piperazine

In tetrahydrofuran (50 ml), cis-1-(4-Bromobenzoyl)-4-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-1-(4-bromobenzoyl)-2,6-dimethylpiperazine (800 mg), diethyl 4-pyridylbolan (255 mg), tetrabutylammonium bromide (275 mg)
20 and tetrakis(triphenylphosphine) palladium (0) (175 mg) were dissolved, followed by the addition of potassium hydroxide (289 mg) and water (0.745 ml). The resulting mixture was heated under reflux for 3 hours. The reaction
25 mixture was concentrated under reduced pressure. Ethyl acetate and water were added to the residue to separate the

organic layer. The organic layer thus obtained was washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by

5 chromatography on a silica gel column (2% methanol - dichloromethane), followed by crystallization from ethanol, whereby the title compound (580 mg, 53%) was obtained as colorless amorphous.

¹H-NMR (DMSO-d₆) δ: 1.33(6H,br), 2.60-2.70(2H,m), 3.40-
10 3.60(2H,m), 3.70-4.10(1H,br), 4.40-4.90(1H,br), 7.02(1H,s), 7.30-7.35(1H,m), 7.45-7.55(3H,m), 7.72(2H,d,J=5.4Hz), 7.75-7.85(3H,m), 8.65(2H,d,J=5.4Hz), 12.43(1H,s).

Elementary analysis for C₂₆H₂₅ClN₄O₃S·0.3H₂O

Calculated: C, 60.70; H, 5.02; Cl, 6.89; N, 10.89; S, 6.23.

15 Found: C, 61.03; H, 5.06; Cl, 7.09; N, 10.51; S, 6.09.

[Example A-105] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In a mixed solvent of dimethoxyethane (10 ml) and methanol (10 ml), 1-[(5-bromopyrimidin-2-yl)carbonyl]-4-
20 [(5-chloroindol-2-yl)sulfonyl]piperazine (485 mg) and 4-pyridylboric acid (197 mg) were suspended at room temperature, followed by the successive addition of tetrakis(triphenylphosphine) palladium (0) (116 mg) and cesium fluoride (1.00 g). The resulting mixture was heated
25 under reflux for 1 week. After the reaction mixture was cooled to room temperature, it was concentrated under

reduced pressure. Dichloromethane and water were added to the concentrate to separate the organic layer. The organic layer thus obtained was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (2% methanol - dichloromethane). The pale yellow crystals precipitated in ethanol were collected by filtration and dissolved in dichloromethane. To the resulting solution, 1N aqueous hydrochloride in ethanol was added and the resulting mixture was distilled under reduced pressure to remove the solvent. The yellow crystals precipitated in ethyl acetate were collected by filtration and dried, whereby the title compound (40%) was obtained.

¹H-NMR (DMSO-d₆) δ: 2.96(2H,br s), 3.16(2H,br s), 3.38(2H,br s), 3.81(2H,br s), 7.05(1H,d,J=2.0Hz), 7.35(1H,dd,J=8.8,2.0Hz), 7.51(1H,d,J=8.8Hz), 7.81(1H,d,J=2.0Hz), 8.13(2H,d,J=5.9Hz), 8.87(2H,d,J=5.9Hz), 9.37(2H,s), 12.48(1H,s).

MS (FAB) m/z: 483 [(M+H)⁺, Cl³⁵], 485 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₁₉ClN₆O₃S·0.9HCl·1.4H₂O

Calculated: C, 48.84; H, 4.23; Cl, 12.45; N, 15.53; S, 5.93.

Found: C, 49.11; H, 4.27; Cl, 12.26; N, 15.34; S,

5.91.

In the same manner as in Example A-6, the compounds

shown in Examples A-106 to A-120 were synthesized.

[Example A-106] 4-[4-[[4-[(6-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

¹H-NMR (CDCl₃) δ: 2.90-4.10(8H,br), 7.02(1H,d,J=1.0Hz),

5 7.22(1H,dd,J=8.8,1.7Hz), 7.46(2H,d,J=8.3Hz), 7.47(1H,s),

7.50(2H,d,J=7.3Hz), 7.60(2H,d,J=8.3Hz), 8.63(1H,d,J=8.8Hz),

8.29(2H,d,J=7.3Hz), 9.32(1H,br s).

Elementary analysis for C₂₄H₂₁ClN₄O₄S·1.7H₂O

Calculated: C, 54.64; H, 4.66; Cl, 6.72; N, 10.62; S, 6.08.

10 Found: C, 54.63; H, 4.65; Cl, 6.91; N, 10.42; S, 6.07.

[Example A-107] 4-[4-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

¹H-NMR (DMSO-d₆) δ: 3.00-3.20(4H,br), 3.34-3.58(2H,br),

3.60-3.84(2H,br), 7.03(1H,s), 7.34(1H,d,J=8.8Hz),

15 7.47(2H,d,J=7.3Hz), 7.51(1H,d,J=8.8Hz), 7.79(2H,d,J=5.9Hz),

7.80(1H,s), 7.81(2H,d,J=7.3Hz), 8.28(2H,d,J=5.9Hz),

12.43(1H,br).

MS (FAB) m/z: 497 [(M+H)⁺, Cl³⁵], 499 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₁ClN₄O₄S·0.2H₂O

20 Calculated: C, 57.59; H, 4.31; Cl, 7.08; N, 11.19; S, 6.41.

Found: C, 57.60; H, 4.38; Cl, 7.26; N, 11.09; S, 6.16.

[Example A-108] 4-[4-[[4-[(5-Chloro-1-methylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

¹H-NMR (CDCl₃) δ: 3.06-3.45(4H,br), 3.48-4.06(4H,br),

25 4.00(3H,s), 7.07(1H,m), 7.33(1H,d,J=8.8Hz),

7.35 (2H, dd, J=8.8, 1.8 Hz), 7.45-7.57 (4H, m),

7.61 (2H, d, J=8.3 Hz), 7.66 (1H, d, J=2.0 Hz), 8.27 (2H, d, J=6.8 Hz).

MS (FAB) m/z: 511 [(M+H)⁺, Cl³⁵], 513 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₅H₂₃ClN₄O₄S·0.9H₂O·0.05CH₂Cl₂

5 Calculated: C, 56.61; H, 4.72; Cl, 7.34; N, 10.54; S, 6.03.

Found: C, 56.51; H, 4.71; Cl, 7.51; N, 10.37; S, 6.29.

[Example A-109] 2-[4-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

¹H-NMR (DMSO-d₆) δ: 3.04-3.18 (4H, br), 3.37-3.83 (4H, br),

10 7.03 (1H, s), 7.33 (1H, d, J=8.8 Hz), 7.38-7.44 (2H, m),

7.45 (2H, d, J=7.3 Hz), 7.50 (1H, d, J=8.8 Hz), 7.61-7.67 (1H, m),

7.80 (1H, s), 7.85 (2H, d, J=7.3 Hz), 8.33 (1H, m), 12.40 (1H, br).

MS (FAB) m/z: 497 [(M+H)⁺, Cl³⁵], 499 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₁ClN₄O₄S·0.2H₂O

15 Calculated: C, 57.59; H, 4.31; Cl, 7.08; N, 11.19; S, 6.41.

Found: C, 57.72; H, 4.58; Cl, 7.13; N, 10.86; S, 6.29.

[Example A-110] 4-[4-[[4-[(5-Chloro-1-ethylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

¹H-NMR (DMSO-d₆) δ: 1.30 (3H, t, J=6.8 Hz), 3.18-3.38 (4H, br),

20 3.40-3.61 (2H, br), 3.62-3.84 (2H, br), 4.46 (2H, q, J=6.8 Hz),

7.16 (1H, s), 7.41 (1H, dd, J=8.8, 2.0 Hz), 7.52 (2H, d, J=7.3 Hz),

7.72 (1H, d, J=8.8 Hz), 7.78-7.88 (5H, m), 8.28 (2H, d, J=7.3 Hz).

MS (FAB) m/z: 525 [(M+H)⁺, Cl³⁵], 527 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₂₅ClN₄O₄S·0.4H₂O

25 Calculated: C, 58.67; H, 4.89; Cl, 6.66; N, 10.53; S, 6.02.

Found: C, 58.73; H, 4.91; Cl, 6.88; N, 10.26; S, 5.96.

[Example A-111] 4-[4-[[4-[(5-Chloro-3-methylbenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

5 $^1\text{H-NMR}$ (DMSO- d_6) δ : 2.67(3H,s), 3.12-3.29(4H,br), 3.37-3.86(4H,br), 7.48(2H,d,J=8.3Hz), 7.65(1H,dd,J=8.8,2.0Hz), 7.80(2H,d,J=7.3Hz), 7.81(2H,d,J=8.3Hz), 8.12(1H,d,J=2.0Hz), 8.15(1H,d,J=8.8Hz), 8.27(2H,d,J=7.3Hz).

MS (FAB) m/z : 528 $[(M+H)^+, \text{Cl}^{35}]$, 530 $[(M+H)^+, \text{Cl}^{37}]$.

10 Elementary analysis for $\text{C}_{25}\text{H}_{22}\text{ClN}_3\text{O}_4\text{S}_2 \cdot 0.7\text{H}_2\text{O}$

Calculated: C, 55.54; H, 4.36; Cl, 6.56; N, 7.77; S, 11.86.

Found: C, 55.73; H, 4.40; Cl, 6.67; N, 7.52; S, 11.72.

[Example A-112] 4-[4-[[cis-4-[(5-Chloroindol-2-yl)sulfonyl]-2,6-dimethylpiperazin-1-

15 yl]carbonyl]phenyl]pyridine N-oxide

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.32(6H,br), 2.60-2.70(2H,m), 3.40-3.60(2H,m), 3.80-4.10(1H,br), 4.50-4.90(1H,br), 7.01(1H,s), 7.30-7.35(1H,m), 7.45-7.55(3H,m), 7.75-7.85(5H,m), 8.27(2H,d,J=6.8Hz), 12.44(1H,s).

20 Elementary analysis for $\text{C}_{26}\text{H}_{25}\text{ClN}_4\text{O}_4\text{S} \cdot 0.5\text{H}_2\text{O}$

Calculated: C, 58.48; H, 4.91; Cl, 6.64; N, 10.49; S, 6.00.

Found: C, 58.68; H, 5.02; Cl, 6.72; N, 10.51; S, 6.04.

[Example A-113] 4-[4-[[4-[(5-Chlorobenzo[b]furan-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

25 $^1\text{H-NMR}$ (CDCl_3) δ : 3.20-3.50(4H,br), 3.50-4.05(4H,br),

7.34 (1H, s), 7.45-7.53 (6H, m), 7.62 (2H, d, J=7.8 Hz),
7.69 (1H, s).

MS (FAB) m/z: 498 [(M+H)⁺, Cl³⁵], 500 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₀ClN₃O₅S·0.25H₂O

5 Calculated: C, 57.37; H, 4.11; Cl, 7.06; N, 8.36; S, 6.38.

Found: C, 57.31; H, 4.30; Cl, 7.17; N, 8.22; S, 6.40.

[Example A-114] 4-[4-[[4-[(6-Chlorobenzo[b]furan-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

¹H-NMR (CDCl₃) δ: 3.20-3.50 (4H, br), 3.50-4.10 (4H, br), 3.65-
10 3.85 (2H, br), 7.35-7.41 (2H, br), 7.46-7.55 (5H, br), 7.58-
7.67 (5H, m), 8.27 (2H, d, J=5.9 Hz).

HRMS (FAB) m/z: 498.0901 (M+H)⁺ (calcd for C₂₄H₂₁ClN₃O₅S
498.0890).

[Example A-115] 4-[4-[[4-[(5-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide
15

¹H-NMR (DMSO-d₆) δ: 3.02-3.90 (8H, m), 7.59 (2H, d, J=8.3 Hz),
7.64 (1H, d, J=2.0 Hz), 8.01-8.05 (3H, m), 8.18 (1H, d, J=2.0 Hz),
8.20 (1H, d, J=8.8 Hz), 8.31 (2H, d, J=6.3 Hz), 8.94 (2H, d, J=6.3 Hz).

MS (FAB) m/z: 514 [(M+H)⁺, Cl³⁵], 516 [(M+H)⁺, Cl³⁷].

20 Elementary analysis for C₂₄H₂₀ClN₃O₃S₂·0.8H₂O

Calculated: C, 54.55; H, 4.12; Cl, 6.71; N, 7.95; S, 12.14.

Found: C, 54.66; H, 4.09; Cl, 6.95; N, 7.77; S, 11.87.

[Example A-116] 4-[4-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

25 ¹H-NMR (DMSO-d₆) δ: 3.16-3.88 (8H, m), 7.48 (2H, d, J=8.3 Hz),

7.58 (1H, dd, J=8.8, 2.0Hz), 7.77 (1H, d, J=7.3Hz), 7.79 (1H, s),
7.81 (2H, d, J=8.8Hz), 8.08 (2H, d, J=8.8Hz), 8.27 (1H, d, J=7.3Hz),
8.33 (1H, s).

MS (FAB) m/z: 514 [(M+H)⁺, Cl³⁵], 516 [(M+H)⁺, Cl³⁷].

5 Elementary analysis for C₂₄H₂₀ClN₃O₄S₂·1.2H₂O

Calculated: C, 53.82; H, 4.22; Cl, 6.62; N, 7.84; S, 11.97.

Found: C, 53.66; H, 4.22; Cl, 6.81; N, 7.61; S, 11.72.

[Example A-117] 2-[4-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

10 ¹H-NMR (DMSO-d₆) δ: 3.06-3.94 (8H, m), 7.38-7.42 (2H, m),
7.46 (2H, d, J=8.3Hz), 7.54-7.63 (2H, m), 7.86 (2H, d, J=8.3Hz),
8.07 (2H, t, J=4.4Hz), 8.27-8.34 (2H, m).

MS (FAB) m/z: 514 [(M+H)⁺, Cl³⁵], 516 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₀ClN₃O₄S₂·0.5H₂O·0.1CH₂Cl₂

15 Calculated: C, 54.56; H, 4.01; Cl, 7.99; N, 7.89; S, 12.04.

Found: C, 54.93; H, 3.95; Cl, 7.90; N, 7.74; S, 11.71.

[Example A-118] 4-[4-[[4-[(5-Chlorobenzothiazol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

20 ¹H-NMR (CDCl₃) δ: 3.40-4.00 (8H, m), 7.50 (2H, d, J=7.3Hz),
7.51 (2H, d, J=8.3Hz), 7.58 (1H, dd, J=8.8, 2.0Hz),
7.63 (2H, d, J=8.3Hz), 7.93 (1H, d, J=8.8Hz), 8.19 (1H, d, J=2.0Hz),
8.27 (2H, d, J=7.3Hz).

MS (FAB) m/z: 515 [(M+H)⁺, Cl³⁵], 517 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₃H₁₉ClN₄O₄S₂·0.1H₂O

25 Calculated: C, 53.45; H, 3.74; Cl, 6.86; N, 10.84; S,

12.41.

Found: C, 53.19; H, 3.72; Cl, 7.09; N, 10.70; S,

12.29.

[Example A-119] 4-[4-[[4-[(6-Chlorobenzothiazol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

¹H-NMR (DMSO-d₆) δ: 3.30-3.85 (8H, m), 7.50 (2H, d, J=8.3 Hz), 7.77 (1H, dd, J=8.8, 2.0 Hz), 7.80 (2H, d, J=7.3 Hz), 7.83 (2H, d, J=8.3 Hz), 8.28 (2H, d, J=7.3 Hz), 8.29 (1H, d, J=8.8 Hz), 8.50 (1H, d, J=2.0 Hz).

MS (FAB) m/z: 515 [(M+H)⁺, Cl³⁵], 517 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₃H₁₉ClN₄O₄S₂

Calculated: C, 53.64; H, 3.72; Cl, 6.88; N, 10.88; S,

12.45.

Found: C, 53.64; H, 3.99; Cl, 6.63; N, 10.90; S,

12.30.

[Example A-120] 4-[4-[[4-[(5-Ethynylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

¹H-NMR (CDCl₃) δ: 2.80-3.90 (8H, br), 4.05 (1H, s), 7.06 (1H, br s), 7.39 (1H, d, J=8.8 Hz), 7.43-7.52 (3H, m), 7.77-7.86 (4H, m), 7.89 (1H, br s), 8.27 (2H, d, J=6.8 Hz), 12.43 (1H, br s).

MS (FAB) m/z: 487 (M+H)⁺.

Elementary analysis for C₂₆H₂₂N₄O₄S·H₂O

Calculated: C, 61.89; H, 4.79; N, 11.10; S, 6.36.

Found: C, 62.00; H, 4.67; N, 11.08; S, 6.35.

[Example A-121] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-

[[2-(pyridin-4-yl)pyrimidin-5-yl]carbonyl]piperazine

In the same manner as in Example A-4, a reaction was effected, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.06(2H,br), 3.14(2H,br), 3.45-
 5 3.85(4H,m), 7.74(1H,d,J=8.3Hz), 7.83(1H,d,J=8.8Hz),
 8.19(1H,d,J=8.3Hz), 8.25-8.29(2H,m), 8.31(2H,d,J=5.9Hz),
 8.52(1H,br s), 8.89(2H,d,J=5.9Hz), 9.02(2H,s).

MS (FAB) m/z: 494 [(M+H)⁺, Cl³⁵], 496 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₀ClN₅O₃S·HCl·H₂O

10 Calculated: C, 52.56; H, 4.23; Cl, 12.93; N, 12.77; S,
 5.85.

Found: C, 52.47; H, 4.20; Cl, 13.09; N, 12.60; S,
 5.98.

[Example A-122] 4-[5-[[4-[(6-Chloronaphthalen-2-
 15 yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine
 N-oxide

In the same manner as in Example A-6, a reaction was effected, whereby the title compound was obtained.

¹H-NMR (CDCl₃) δ: 3.05-3.30(4H,br), 3.55-4.00(4H,br),
 20 7.61(1H,dd,J=8.3 and 2.0Hz), 7.76(1H,dd,J=8.8 and 2.0Hz),
 7.91-7.97(3H,m), 8.25-8.29(2H,m), 8.31-8.35(3H,m),
 8.77(2H,s).

MS (FAB) m/z: 510 [(M+H)⁺, Cl³⁵], 512 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₀ClN₅O₄S·0.8H₂O

25 Calculated: C, 54.97; H, 4.15; Cl, 6.76; N, 13.36; S, 6.11.

Found: C, 54.99; H, 4.08; Cl, 6.75; N, 13.24; S, 6.20.

[Example A-123] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-105, the title
5 compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.94(2H, br s), 3.13(2H, br s),
3.37(2H, br s), 3.80(2H, br s), 7.74(1H, dd, J=8.8, 2.4 Hz),
7.83(1H, dd, J=8.8, 2.0 Hz), 8.05-8.18(2H, br),
8.19(1H, d, J=8.8 Hz), 8.25-8.32(2H, m), 8.52(1H, br s), 8.82-
10 8.91(2H, br), 9.33-9.38(2H, m).

MS (FAB) m/z: 494 [(M+H)⁺, Cl³⁵], 496 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₀ClN₅O₃S·0.95HCl·0.5H₂O

Calculated: C, 53.62; H, 4.12; Cl, 12.86; N, 13.03; S,
5.96.

15 Found: C, 53.50; H, 4.09; Cl, 12.76; N, 12.87; S,
5.91.

[Example A-124] 4-[2-[[4-[(6-Chloronaphthalen-2-
yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine
N-oxide

20 In the same manner as in Example A-6, the title
compound was obtained.

¹H-NMR (CDCl₃) δ: 3.14-3.17(2H, m), 3.25-3.28(2H, m), 3.55-
3.58(2H, m), 3.94-3.98(2H, m), 7.50(2H, d, J=7.3 Hz),
7.60(1H, dd, J=8.8, 2.0 Hz), 7.76(1H, dd, J=8.8, 2.0 Hz), 7.91-
25 7.96(3H, m), 8.30-8.35(3H, m), 8.98(2H, s).

MS (FAB) m/z : 510 $[(M+H)^+, Cl^{35}]$, 512 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{24}H_{20}ClN_5O_4S \cdot 0.6H_2O$

Calculated: C, 55.35; H, 4.10; Cl, 6.81; N, 13.45; S, 6.16.

Found: C, 55.01; H, 4.01; Cl, 7.00; N, 13.28; S, 6.28.

5 [Example A-125] 4-[4-[[4-[(6-Bromonaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-1, the title compound was obtained using 4-[4-[(piperazin-1-yl)carbonyl]phenyl]pyridine N-oxide hydrochloride and (6-bromonaphthalen-2-yl)sulfonyl chloride as starting materials.

1H -NMR ($CDCl_3$) δ : 2.80-3.40 (4H, br), 3.40-4.05 (4H, br), 7.43 (2H, d, $J=7.8$ Hz), 7.47 (2H, d, $J=7.1$ Hz), 7.58 (2H, d, $J=7.8$ Hz), 7.70-7.78 (2H, m), 7.85 (1H, d, $J=8.8$ Hz), 7.92 (1H, d, $J=8.8$ Hz), 8.13 (1H, s), 8.26 (2H, d, $J=7.1$ Hz), 8.30 (1H, s).

MS (FAB) m/z : 552 $[(M+H)^+, Br^{79}]$, 554 $[(M+H)^+, Br^{81}]$.

Elementary analysis for $C_{26}H_{22}BrN_3O_4S \cdot 0.5H_2O$

Calculated: C, 55.62; H, 4.13; N, 7.48; Br, 14.23; S, 5.71.

Found: C, 55.36; H, 3.89; N, 7.41; Br, 14.20; S, 5.59.

20 [Example A-126] 1-[(6-Bromonaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example A-1, a reaction was effected, whereby the title compound was obtained.

1H -NMR ($CDCl_3$) δ : 2.80-3.40 (4H, br), 3.40-4.10 (4H, br), 7.43 (2H, d, $J=8.3$ Hz), 7.47 (2H, d, $J=5.6$ Hz), 7.63 (2H, d, $J=8.3$ Hz),

7.72-7.78 (2H, m), 7.86 (1H, d, J=8.8 Hz), 7.92 (1H, d, J=8.8 Hz),
8.13 (1H, d, J=1.5 Hz), 8.30 (1H, s), 8.68 (2H, d, J=5.6 Hz).

MS (FAB) m/z: 536 [(M+H)⁺, Br⁷⁹], 538 [(M+H)⁺, Br⁸¹].

Elementary analysis for C₂₆H₂₂BrN₃O₃S·0.5H₂O

5 Calculated: C, 57.25; H, 4.25; N, 7.70; Br, 14.65; S, 5.88.

Found: C, 57.51; H, 3.96; N, 7.67; Br, 14.76; S, 6.01.

[Example A-127] 1-[(6-Ethynylnaphthalen-2-yl)sulfonyl]-4-
[4-(pyridin-4-yl)benzoyl]piperazine

To a solution of 1-[(6-bromonaphthalen-2-yl)sulfonyl]-
10 4-[4-(pyridin-4-yl)benzoyl]piperazine (310 mg) and
triphenylphosphine (455 mg) in tetrahydrofuran (1.0 ml),
triethylamine (3.0 ml), N,N-dimethylformamide (1.0 ml),
trimethylsilylacetylene (130 ml) and palladium acetate
(13.0 mg) were added, followed by heating under reflux for
15 2 hours. After the reaction mixture was allowed to cool
down to room temperature, dichloromethane (15 ml) and water
(30 ml) were added to separate the organic layer. The
organic layer thus obtained was dried over anhydrous sodium
sulfate and distilled under reduced pressure to remove the
20 solvent. The residue was purified by chromatography on a
silica gel column (dichloromethane : acetone = 3:1),
whereby colorless amorphous was obtained. The resulting
product was dissolved in methanol (25 ml), followed by the
addition of tetrahydrofuran (5.0 ml) and potassium
25 carbonate (300 mg). The resulting mixture was stirred for
30 minutes. Dichloromethane (30 ml) and water (50 ml) were

added to the reaction mixture to separate the organic layer. The organic layer thus obtained was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified
 5 by chromatography on a silica gel column (dichloromethane : acetone = 4:1), followed by pulverization and washing in a mixed solvent of dichloromethane, acetone and water, whereby the title compound (210 mg, 75%) was obtained.

¹H-NMR (CDCl₃) δ: 2.80-4.10 (8H, br), 7.43 (2H, d, J=8.3Hz),
 10 7.47 (2H, d, J=6.4Hz), 7.67 (2H, d, J=8.3Hz),
 7.68 (1H, dd, J=8.8, 1.5Hz), 7.75 (1H, dd, J=8.3, 1.5Hz),
 7.93 (1H, d, J=8.3Hz), 7.97 (1H, d, J=8.8Hz), 8.11 (1H, s),
 8.30 (1H, s), 8.68 (2H, d, J=6.4Hz).

MS (FAB) m/z: 482 (M+H)⁺.

15 Elementary analysis for C₂₈H₂₃N₃O₃S·0.4H₂O

Calculated: C, 68.81; H, 4.91; N, 8.60; S, 6.56.

Found: C, 68.96; H, 4.91; N, 8.47; S, 6.52.

[Example A-128] 4-[4-[[4-[(6-Ethynylnaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

20 In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.95-4.00 (8H, br), 7.42 (2H, d, J=8.3Hz),
 7.46 (2H, d, J=6.8Hz), 7.58 (2H, d, J=8.3Hz),
 7.68 (1H, dd, J=8.8, 1.5Hz), 7.75 (1H, dd, J=8.3, 1.5Hz),
 25 7.92 (1H, d, J=8.8Hz), 7.95 (1H, d, J=8.3Hz), 8.10 (1H, s),

8.25 (2H, d, J=6.8 Hz), 8.30 (1H, s).

MS (FAB) m/z: 498 [(M+H)⁺].

Elementary analysis for C₂₈H₂₃N₃O₄S·H₂O

Calculated: C, 65.23; H, 4.89; N, 8.15; S, 6.22.

5 Found: C, 65.41 H, 5.14; N, 8.19; S, 6.11.

[Example A-129] 2-Carbamoylmethyl-4-[(5-chloro-1-phenylsulfonyl-5-chloroindol-2-ylsulfonyl)-1-[4-(pyridin-4-yl)benzoyl]piperazine

10 In the same manner as in Example A-7 or Example A-1, a reaction was effected, whereby the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.44-3.28 (4H, m), 3.50-4.14 (2H, m), 4.45-4.78 (1H, m), 5.58-5.79 (1H, m), 7.44-7.65 (13H, m), 7.69 (2H, d, J=8.3 Hz), 8.05 (2H, d, J=8.3 Hz), 8.13-8.17 (1H, m), 15 8.69 (2H, d, J=5.9 Hz).

MS (FAB) m/z: 678 [(M+H)⁺, Cl³⁵], 680 [(M+H)⁺, Cl³⁷].

[Example A-130] 2-Carbamoylmethyl-4-[(5-chloroindol-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

20 In the same manner as in Example A-99, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.55-2.80 (2H, m), 3.00-4.56 (6H, m), 5.05-5.17 (1H, m), 6.90-7.05 (2H, m), 7.34 (1H, dd, J=8.8, 2.2 Hz), 7.40-7.63 (4H, m), 7.79 (1H, m), 7.99 (1H, m), 8.24 (2H, br), 8.90 (1H, m), 12.43 (1H, s).

25 MS (FAB) m/z: 538 [(M+H)⁺, Cl³⁵], 540 [(M+H)⁺, Cl³⁷].

Elementary analysis for $C_{26}H_{24}ClN_5O_4S \cdot 1.2HCl \cdot 2.5H_2O$

Calculated: C, 49.82; H, 4.86; Cl, 12.44; N, 11.17; S, 5.12.

Found: C, 50.14; H, 5.07; Cl, 12.54; N, 10.80; S, 5.18.

[Example A-131] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[2-(pyridin-4-yl)pyrimidin-5-yl]carbonyl]piperazine

In the same manner as in Example A-4, a reaction was effected, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.08(2H,br), 3.18(2H,br), 3.52(2H,br), 3.77(2H,br), 7.04(1H,d,J=1.5Hz), 7.34(1H,dd,J=8.8,2.0Hz), 7.50(1H,d,J=8.8Hz), 7.80(1H,d,J=2.0Hz), 8.48-8.53(2H,m), 8.91-8.95(2H,m), 9.07(2H,s), 12.46(1H,br s).

MS (FAB) m/z: 483 [(M+H)⁺, Cl³⁵], 485 [(M+H)⁺, Cl³⁷].

Elementary analysis for $C_{22}H_{19}ClN_6O_3S \cdot HCl \cdot 1.3H_2O \cdot 0.2EtOH$
Calculated: C, 48.74; H, 4.35; Cl, 12.84; N, 15.22; S, 5.81.

Found: C, 48.87; H, 4.38; Cl, 12.82; N, 15.02; S, 5.86.

[Example A-132] 1-[(6-Chlorobenzothiophen-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-105, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.03-3.06(2H,m), 3.20-3.23(2H,m), 3.41-3.44(2H,m), 3.83-3.86(2H,m), 7.61(1H,dd,J=8.8,2.0Hz),

8.10 (1H, d, J=8.8Hz), 8.13 (1H, s), 8.30-8.40 (3H, m), 8.90-9.02 (2H, br), 9.40-9.46 (2H, m).

MS (FAB) m/z: 500 [(M+H)⁺, Cl³⁵], 502 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₁₈ClN₅O₃S·HCl·0.7H₂O

5 Calculated: C, 48.13; H, 3.74; Cl, 12.91; N, 12.75; S, 11.68.

Found: C, 47.95; H, 3.78; Cl, 13.13; N, 12.65; S, 11.53.

[Example A-133] 4-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine
10 N-oxide

In the same manner as in Example A-6, a reaction was effected, whereby the title compound was obtained.

¹H-NMR (CDCl₃) δ: 3.24 (2H, br), 3.34 (2H, br), 3.60 (2H, br),
15 3.98 (2H, br), 7.47 (1H, dd, J=8.8, 2.0Hz), 7.52 (2H, d, J=7.3Hz), 7.79 (1H, s), 7.83 (1H, d, J=8.8Hz), 7.88 (1H, br s), 8.33 (2H, d, J=7.3Hz), 9.00 (2H, s).

MS (FAB) m/z: 516 [(M+H)⁺, Cl³⁵], 518 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₁₈ClN₅O₄S·0.4H₂O

20 Calculated: C, 50.50; H, 3.62; Cl, 6.78; N, 13.39; S, 12.26.

Found: C, 50.24; H, 3.62; Cl, 7.14; N, 13.19; S, 12.04.

[Example A-134] 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine
25 N-oxide

In the same manner as in Example A-6, a reaction was effected, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.95(2H,br), 3.15(2H,br), 3.37(2H,br), 3.79(2H,br), 7.05(1H,s), 7.34(1H,dd,J=8.8,1.5Hz), 7.51(1H,d,J=8.8Hz), 7.80(1H,d,J=1.5Hz), 7.95(2H,d,J=7.3Hz), 8.37(2H,d,J=7.3Hz), 9.28(2H,s), 12.47(1H,s).

MS (FAB) m/z: 499 [(M+H)⁺, Cl³⁵], 501 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₁₉ClN₆O₄S·0.5H₂O·0.2EtOH

Calculated: C, 52.02; H, 4.13; Cl, 6.86; N, 16.25; S, 6.20.

Found: C, 52.03; H, 3.99; Cl, 7.18; N, 15.99; S, 6.16.

[Example A-135] 4-[5-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

In the same manner as in Example A-6, a reaction was effected, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.09(2H,br), 3.16(2H,br), 3.53(2H,br), 3.75(2H,br), 7.03(1H,s), 7.32(1H,dd,J=8.8,2.0Hz), 7.50(1H,d,J=8.8Hz), 7.79(1H,d,J=2.0Hz), 8.27(2H,d,J=7.3Hz), 8.34(2H,d,J=7.3Hz), 8.95(2H,s), 12.42(1H,br s).

MS (FAB) m/z: 499 [(M+H)⁺, Cl³⁵], 501 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₁₉ClN₆O₄S·H₂O

Calculated: C, 51.11; H, 4.09; Cl, 6.86; N, 16.26; S, 6.20.

Found: C, 51.29; H, 4.34; Cl, 6.80; N, 15.90; S, 6.08.

[Example A-136] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-105, the title compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.20 (2H, t, $J=4.9\text{Hz}$), 3.62-3.78 (2H, m),
3.45-3.60 (2H, m), 3.78 (2H, t, $J=4.9\text{Hz}$), 4.63 (2H, s),
5 4.64 (2H, s), 7.35 (1H, d, $J=8.3\text{Hz}$), 7.38 (1H, d, $J=8.3\text{Hz}$),
7.42 (1H, s), 8.22 (2H, d, $J=5.4\text{Hz}$), 8.92 (2H, d, $J=5.4\text{Hz}$),
9.44 (2H, s).

MS (FAB) m/z : 485 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 487 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{22}\text{H}_{21}\text{ClN}_6\text{O}_3\text{S}\cdot\text{HCl}\cdot 1.8\text{H}_2\text{O}$

10 Calculated: C, 47.71; H, 4.66; Cl, 12.80; N, 15.17; S,
5.79.

Found: C, 48.01; H, 4.39; Cl, 13.19; N, 14.74; S,
5.73.

In the same manner as in Example A-4, the compounds
15 shown in Examples A-137 and A-138 were synthesized.

[Example A-137] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
[[5-(pyridin-4-yl)pyrazin-2-yl]carbonyl]piperazine

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.01 (2H, br), 3.14 (2H, br), 3.62 (2H, br),
3.81 (2H, br), 7.74 (1H, dd, $J=8.8, 2.0\text{Hz}$),
20 7.84 (1H, dd, $J=8.8, 2.0\text{Hz}$), 8.19 (1H, d, $J=8.8\text{Hz}$), 8.25-
8.31 (2H, m), 8.46 (2H, d, $J=5.4\text{Hz}$), 8.52 (1H, br s), 8.91 (3H, m),
9.47 (1H, s).

MS (FAB) m/z : 494 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 496 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{24}\text{H}_{20}\text{ClN}_5\text{O}_3\text{S}\cdot\text{HCl}\cdot\text{H}_2\text{O}\cdot 0.2\text{AcOEt}$

25 Calculated: C, 52.62; H, 4.38; Cl, 12.53; N, 12.37; S,

5.66.

Found: C, 52.47; H, 4.51; Cl, 12.87; N, 12.09; S,

5.68.

[Example A-138] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-
5 (pyridin-4-yl)pyrazin-2-yl]carbonyl]piperazine

¹H-NMR (DMSO-d₆) δ: 3.04(2H,br), 3.18(2H,br), 3.63(2H,br),
3.81(2H,br), 7.05(1H,s), 7.33(1H,dd,J=8.8,2.0Hz),
7.50(1H,d,J=8.8Hz), 7.79(1H,d,J=2.0Hz), 8.11(2H,d,J=6.4Hz),
8.77(2H,d,J=6.4Hz), 8.93(1H,d,J=1.5Hz), 9.34(1H,d,J=1.5Hz),
10 12.43(1H,br s).

MS (FAB) m/z: 483 [(M+H)⁺, Cl³⁵], 485 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₁₉ClN₆O₃S·H₂O

Calculated: C, 52.75; H, 4.23; Cl, 7.08; N, 16.78; S, 6.40.

Found: C, 52.78; H, 4.27; Cl, 7.17; N, 16.67; S, 6.37.

15 In the same manner as in Example A-6, reaction was
effected, whereby the compounds shown in Examples A-139 and
A-140 were synthesized.

[Example A-139] 4-[5-[[4-[(6-Chloronaphthalen-2-
yl)sulfonyl]piperazin-1-yl]carbonyl]pyrazin-2-yl]pyridine

20 N-oxide

¹H-NMR (CDCl₃) δ: 3.19(2H,br), 3.26(2H,br), 3.88(2H,br),
3.94(2H,br), 7.59(1H,dd,J=8.8,2.0Hz),
7.78(1H,dd,J=8.8,2.0Hz), 7.91-7.95(3H,m),
7.98(2H,d,J=7.3Hz), 8.30(2H,d,J=7.3Hz), 8.32(1H,d,J=2.0Hz),
25 8.90(1H,d,J=1.5Hz), 8.99(1H,d,J=1.5Hz).

MS (FAB) m/z: 510 [(M+H)⁺, Cl³⁵], 512 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₀ClN₅O₄S·1.1H₂O

Calculated: C, 54.41; H, 4.22; Cl, 6.69; N, 13.22; S, 6.05.

Found: C, 54.27; H, 4.61; Cl, 6.99; N, 13.28; S, 6.12.

5 [Example A-140] 4-[5-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrazin-2-yl]pyridine N-oxide

¹H-NMR (DMSO-d₆) δ: 3.03(2H,br), 3.17(2H,br), 3.63(2H,br),
3.80(2H,br), 7.04(1H,s), 7.33(1H,dd,J=8.8,2.0Hz),
10 7.50(1H,d,J=8.8Hz), 7.80(1H,d,J=2.0Hz), 8.19(2H,d,J=7.3Hz),
8.37(2H,d,J=7.3Hz), 8.87(1H,d,J=1.5Hz), 9.31(1H,d,J=1.5Hz),
12.45(1H,br s).

MS (FAB) m/z: 499 [(M+H)⁺, Cl³⁵], 501 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₁₉ClN₆O₄S·H₂O

15 Calculated: C, 51.11; H, 4.09; Cl, 6.86; N, 16.26; S, 6.20.

Found: C, 50.92; H, 4.05; Cl, 6.96; N, 15.88; S, 6.10.

[Example A-141] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(3-methylpyridin-4-yl)benzoyl]piperazine hydrochloride

20 In the same manner as in Example A-4, a reaction was effected, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.36(3H,s), 2.95-3.30(4H,br), 3.35-
3.90(4H,br), 7.50(2H,d,J=8.8Hz), 7.53(2H,d,J=8.8Hz),
7.71(1H,d,J=5.4Hz), 7.73(1H,dd,J=8.8,2.0Hz),
7.83(1H,dd,J=8.8,2.0Hz), 8.18(1H,d,J=8.8Hz), 8.24-
25 8.30(2H,m), 8.50(1H,br s), 8.72(1H,d,J=5.4Hz), 8.80(1H,s).

MS (FAB) m/z: 506 [(M+H)⁺, Cl³⁵], 508 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₇H₂₄ClN₃O₃S·0.8HCl·1.5H₂O

Calculated: C, 57.68; H, 4.98; Cl, 11.35; N, 7.48; S, 5.70.

Found: C, 57.50; H, 5.06; Cl, 11.35; N, 7.28; S, 5.95.

5 [Example A-142] 4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-3-methylpyridine N-oxide

In the same manner as in Example A-6, a reaction was effected, whereby the title compound was obtained.

10 ¹H-NMR (CDCl₃) δ: 2.21(3H,s), 3.14(4H,br), 3.68(2H,br), 3.85(2H,br), 7.09(1H,d,J=6.8Hz), 7.32(2H,d,J=8.3Hz), 7.41(2H,d,J=8.3Hz), 7.60(1H,dd,J=8.8,2.0Hz), 7.77(1H,dd,J=8.8,2.0Hz), 7.90-7.96(3H,m), 8.11(1H,dd,J=6.4,1.5Hz), 8.15(1H,br s), 8.31(1H,br s).

15 MS (FAB) m/z: 522 [(M+H)⁺, Cl³⁵], 524 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₇H₂₄ClN₃O₄S·0.1H₂O

Calculated: C, 61.92; H, 4.66; Cl, 6.77; N, 8.02; S, 6.12.

Found: C, 61.76; H, 4.72; Cl, 7.04; N, 7.76; S, 6.30.

20 [Example A-143] 1-(4-Amidinobenzoyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Example A-4, a reaction was effected, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.03(2H,br s), 3.13(2H,br s), 3.30(2H,br s), 3.73(2H,br s), 7.56(2H,d,J=8.3Hz),

25 7.73(1H,dd,J=8.8,2.0Hz), 7.78-7.85(3H,m),

8.18 (1H, d, J=8.3Hz), 8.25-8.30 (2H, m), 8.50 (1H, s), 9.10 (2H, br s), 9.38 (2H, br s).

MS (FAB) m/z: 457 [(M+H)⁺, Cl³⁵], 459 [(M+H)⁺, Cl³⁷].

[Example A-144] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-

5 [4-(4,5-dihydroimidazol-2-yl)benzoyl]piperazine

¹H-NMR (DMSO-d₆) δ: 3.04 (2H, br s), 3.13 (2H, br s),

3.37 (2H, br s), 3.74 (2H, br s), 4.00 (4H, s),

7.60 (2H, d, J=8.3Hz), 7.73 (1H, dd, J=8.8, 2.0Hz),

7.83 (1H, d, J=8.8Hz), 8.11 (2H, d, J=8.3Hz), 8.19 (1H, d, J=8.8Hz),

10 8.26 (1H, d, J=2.0Hz), 8.28 (1H, d, J=8.8Hz), 8.50 (1H, s),

11.00 (2H, br s).

MS (FAB) m/z: 483 [(M+H)⁺, Cl³⁵], 485 [(M+H)⁺, Cl³⁷].

[Example A-145] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-

[4-[2-(N-tert-butoxycarbonylamino)pyridin-4-

15 yl]benzoyl]piperazine

In the same manner as in Example A-4, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.54 (9H, s), 3.00-3.30 (4H, m), 3.40-

4.10 (4H, m), 7.14 (1H, dd, J=5.4, 1.5Hz), 7.38 (2H, d, J=8.3Hz),

20 7.53 (1H, br s), 7.60 (1H, dd, J=8.8, 2.0Hz), 7.67 (2H, d, J=8.3Hz),

7.77 (1H, dd, J=8.3, 1.5Hz), 7.91-7.98 (3H, m),

8.18 (1H, d, J=1.5Hz), 8.29 (1H, d, J=5.4Hz), 8.32 (1H, s).

[Example A-146] 1-[4-(2-Aminopyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

25 In the same manner as in Example A-7, the title

compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.95-3.25 (4H,m), 3.30-3.93 (4H,m), 7.14-7.23 (2H,m), 7.51 (2H,d,J=8.3Hz), 7.66-7.75 (1H,m), 7.76 (2H,d,J=8.8Hz), 7.82 (1H,m), 8.03 (1H,d,J=6.8Hz), 8.05-8.12 (2H,m), 8.13-8.30 (3H,m), 8.50 (1H,s), 13.60 (1H,br).
 5 MS (FAB) m/z: 507 [(M+H)⁺, Cl³⁵], 509 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₂₃ClN₄O₃S · HCl · 3.6H₂O

Calculated: C, 51.34; H, 5.17; Cl, 11.66; N, 9.21; S, 5.27.

Found: C, 51.07; H, 5.24; Cl, 11.85; N, 9.10; S, 5.75.

10 [Example A-147] 2-tert-Butoxycarbonylamino-4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

15 ¹H-NMR (CDCl₃) δ: 1.55 (9H,s), 2.95-3.35 (4H,br), 3.50-4.00 (4H,m), 7.11 (1H,dd,J=6.8,2.5Hz), 7.40 (2H,d,J=8.3Hz), 7.60 (1H,dd,J=8.8,2.0Hz), 7.64 (2H,d,J=8.3Hz), 7.77 (1H,dd,J=8.8,2.0Hz), 7.91-7.98 (3H,m), 8.25 (1H,d,J=6.8Hz), 8.31 (1H,d,J=2.0Hz), 8.42 (1H,d,J=2.5Hz),
 20 9.28 (1H,s).

MS (FAB) m/z: 623 [(M+H)⁺, Cl³⁵], 625 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₃₁H₃₁ClN₄O₆S · 0.1H₂O

Calculated: C, 59.58; H, 5.03; Cl, 5.67; N, 8.97; S, 5.13.

Found: C, 59.43; H, 5.04; Cl, 5.95; N, 8.89; S, 5.17.

25 [Example A-148] 2-Amino-4-[4-[[4-[(6-chloronaphthalen-2-

yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-7, the title compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.95-3.25 (4H, br), 3.30-3.90 (4H, m),

5 7.14 (1H, dd, $J=6.8, 2.0\text{Hz}$), 7.28 (1H, d, $J=2.0\text{Hz}$),

7.49 (2H, d, $J=8.3\text{Hz}$), 7.70-7.78 (3H, m),

7.82 (1H, dd, $J=8.8, 2.0\text{Hz}$), 8.16 (2H, br), 8.18 (1H, d, $J=8.8\text{Hz}$),

8.25-8.30 (2H, m), 8.32 (1H, d, $J=6.8\text{Hz}$), 8.50 (1H, br s).

MS (FAB) m/z : 523 $[(M+H)^+, \text{Cl}^{35}]$, 525 $[(M+H)^+, \text{Cl}^{37}]$.

10 Elementary analysis for $\text{C}_{26}\text{H}_{23}\text{ClN}_4\text{O}_4\text{S}\cdot\text{HCl}\cdot 1.5\text{H}_2\text{O}$

Calculated: C, 53.25; H, 4.64; Cl, 12.09; N, 9.55; S, 5.47.

Found: C, 53.21; H, 4.67; Cl, 11.96; N, 9.53; S, 5.61.

[Example A-149] 4-[5-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyridin-2-yl]pyridine

15 N-oxide

In the same manner as in Example A-6, the title compound was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.00-3.40 (4H, br s), 3.50-4.05 (4H, m),

7.61 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.73-7.83 (3H, m), 7.90-7.97 (5H, m),

20 8.27 (2H, d, $J=7.3\text{Hz}$), 8.31 (1H, br s), 8.63 (1H, m).

MS (FAB) m/z : 509 $[(M+H)^+, \text{Cl}^{35}]$, 511 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{25}\text{H}_{21}\text{ClN}_4\text{O}_4\text{S}\cdot 0.5\text{H}_2\text{O}$

Calculated: C, 57.97; H, 4.28; Cl, 6.84; N, 10.82; S, 6.19.

Found: C, 57.99; H, 4.51; Cl, 6.99; N, 10.54; S, 6.53.

25 [Example A-150] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-

[[1-oxo-6-(1-oxopyridin-4-yl)pyridin-3-yl]carbonyl]piperazine

In the same manner as in Example A-6, the title compound was obtained.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 3.15(4H, br s), 3.50-4.00(4H, m), 7.20-7.30(1H, m), 7.52(1H, d, $J=8.3\text{Hz}$), 7.61(1H, dd, $J=8.8, 2.0\text{Hz}$), 7.76(1H, dd, $J=8.8, 2.0\text{Hz}$), 7.89(2H, d, $J=7.3\text{Hz}$), 7.91-7.97(3H, m), 8.21(1H, d, $J=1.5\text{Hz}$), 8.26(2H, d, $J=7.3\text{Hz}$), 8.31(1H, br s).

10 MS (FAB) m/z : 525 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 527 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{25}\text{H}_{21}\text{ClN}_4\text{O}_5\text{S}\cdot 0.1\text{H}_2\text{O}$

Calculated: C, 57.00; H, 4.06; Cl, 6.73; N, 10.64; S, 6.09.

Found: C, 57.03; H, 4.23; Cl, 6.82; N, 10.34; S, 6.15.

[Example A-151] 1-[4-(2-Acetoxymethylpyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine
15 hydrochloride

In acetic anhydride (25 ml), 4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-methylpyridine N-oxide (900 mg) was
20 dissolved, followed by heating under reflux for 15 minutes. Ethanol (25 ml) was added to the reaction mixture and the resulting mixture was heated under reflux for further 1 hour. To the reaction mixture, dichloromethane and an aqueous solution of sodium bicarbonate were added to
25 separate the organic layer. The organic layer thus obtained was dried over anhydrous sodium sulfate and

concentrated under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (dichloromethane ~ 1.5% methanol - dichloromethane), followed by crystallization from ethanol. The crystals
 5 were dissolved in dichloromethane and the resulting solution was made acidic by the addition of hydrochloric acid in ethanol. The resulting acidic mixture was concentrated, whereby the title compound (842 mg, 87%, pale yellow powder) was obtained.

10 $^1\text{H-NMR}$ (DMSO-d_6) δ : 2.12 (3H, s), 3.06 (4H, br), 3.30-3.80 (4H, br), 5.23 (2H, s), 7.48 (2H, d, $J=8.3\text{Hz}$), 7.72 (1H, dd, $J=8.8, 2.4\text{Hz}$), 7.78 (1H, d, $J=5.4\text{Hz}$), 7.79-7.87 (4H, m), 8.17 (1H, d, $J=8.8\text{Hz}$), 8.23-8.29 (2H, m), 8.49 (1H, br s), 8.67 (1H, d, $J=5.4\text{Hz}$).

15 MS (FAB) m/z : 564 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 566 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{29}\text{H}_{26}\text{ClN}_3\text{O}_5\text{S}\cdot 0.4\text{HCl}\cdot 0.7\text{H}_2\text{O}$

Calculated: C, 58.91; H, 4.74; Cl, 8.39; N, 7.11; S, 5.42.

Found: C, 58.86; H, 4.69; Cl, 8.29; N, 6.99; S, 5.41.

[Example A-152] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(2-hydroxymethylpyridin-4-yl)benzoyl]piperazine
 20

In the same manner as in Example A-3, the title compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.08 (4H, br), 3.47 (2H, br), 3.71 (2H, br), 4.66 (2H, s), 7.49 (2H, d, $J=8.3\text{Hz}$), 7.64 (1H, d, $J=5.4\text{Hz}$),
 25 7.73 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.78-7.85 (4H, m),

8.18 (1H, d, J=8.8Hz), 8.23-8.30 (2H, m), 8.50 (1H, br s),
8.58 (1H, d, J=5.4Hz).

MS (FAB) m/z: 522 [(M+H)⁺, Cl³⁵], 524 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₇H₂₄ClN₃O₄S·0.25HCl·1.2H₂O

5 Calculated: C, 58.67; H, 4.86; Cl, 8.02; N, 7.60; S, 5.80.

Found: C, 58.73; H, 4.77; Cl, 7.94; N, 7.39; S, 5.82.

[Example A-153] 2-Acetoxymethyl-4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

10 In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.21 (3H, s), 3.14 (4H, br), 3.30-
4.10 (4H, br), 5.42 (2H, s), 7.40-7.46 (3H, m), 7.54-7.64 (4H, m),
7.76 (1H, d, J=7.3Hz), 7.90-7.97 (3H, m), 8.29 (1H, d, J=6.4Hz),
15 8.31 (1H, br s).

MS (FAB) m/z: 580 [(M+H)⁺, Cl³⁵], 582 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₉H₂₆ClN₃O₆S·0.3H₂O

Calculated: C, 59.49; H, 4.58; Cl, 6.06; N, 7.18; S, 5.48.

Found: C, 59.33; H, 4.63; Cl, 6.18; N, 7.26; S, 5.49.

20 [Example A-154] 4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-hydroxymethylpyridine N-oxide

In the same manner as in Example A-3, the title compound was obtained.

25 ¹H-NMR (CDCl₃) δ: 3.06 (4H, br), 3.30-3.90 (4H, br),

4.63 (2H, d, J=5.4 Hz), 5.66 (1H, t, J=5.4 Hz), 7.46 (2H, d, J=8.3 Hz),
 7.70 (1H, dd, J=6.8, 2.9 Hz), 7.73 (1H, dd, J=8.8, 2.0 Hz),
 7.78 (2H, d, J=8.3 Hz), 7.80-7.84 (2H, m), 8.18 (1H, d, J=8.8 Hz),
 8.25-8.32 (3H, m), 8.50 (1H, br s).

5 MS (FAB) m/z: 538 [(M+H)⁺, Cl³⁵], 540 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₇H₂₄ClN₃O₅S·0.4H₂O

Calculated: C, 59.48; H, 4.58; Cl, 6.50; N, 7.71; S, 5.88.

Found: C, 59.60; H, 4.56; Cl, 6.50; N, 7.52; S, 5.92.

[Example A-155] 1-[4-(2-Aminomethylpyridin-4-yl)benzoyl]-
 10 4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine
 hydrochloride

At room temperature, 1-[4-(2-azidomethylpyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine
 (159 mg) was dissolved in tetrahydrofuran (5 ml), followed
 15 by the addition of water (0.5 ml) and triphenylphosphine
 (114 mg). The resulting mixture was stirred for 18 hours.
 The residue obtained by distilling off the solvent under
 reduced pressure was purified by chromatography on a silica
 gel column (10% methanol - dichloromethane), followed by
 20 dissolution in dichloromethane. To the resulting solution,
 1N hydrochloric acid in ethanol and water were added. The
 resulting mixture was then concentrated. The crystals were
 collected by filtration and washed with ethyl acetate,
 whereby the title compound (53 mg, 30%) was obtained.

25 ¹H-NMR (DMSO-d₆) δ: 3.07 (4H, br), 3.30-4.20 (4H, m),
 4.24 (1H, d, J=5.8 Hz), 4.27 (1H, d, J=5.8 Hz), 7.51 (2H, d, J=8.3 Hz),

7.71-7.78 (2H,m), 7.80-7.87 (3H,m), 7.89 (1H,br s),
8.19 (1H,d,J=8.8Hz), 8.25-8.30 (2H,m), 8.42 (2H,br s),
8.50 (1H,br s), 8.69 (1H,d,J=5.4Hz).
MS (FAB) m/z: 521 [(M+H)⁺, Cl³⁵], 523 [(M+H)⁺, Cl³⁷].

5 Elementary analysis for C₂₇H₂₅ClN₄O₃S·1.5HCl·2.1H₂O
Calculated: C, 52.85; H, 5.04; Cl, 14.45; N, 9.13; S, 5.23.
Found: C, 52.69; H, 4.93; Cl, 14.60; N, 9.21; S, 5.25.
[Example A-156] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
[4-[2-(dimethylaminomethyl)pyridin-4-yl]benzoyl]piperazine
10 hydrochloride

In the same manner as in Referential Example 178, the
corresponding bromo compound was obtained using 1-[(6-
chloronaphthalen-2-yl)sulfonyl]-4-[4-(2-
hydroxymethylpyridin-4-yl)benzoyl]piperazine (300 mg). To
15 the resulting compound, dimethylamine hydrochloride (469
mg) and potassium carbonate (795 mg) were added, followed
by stirring for 24 hours. The solvent was then distilled
off under reduced pressure. Ethyl acetate and water were
added to the residue to separate the organic layer. The
20 organic layer thus obtained was dried over anhydrous sodium
sulfate. The residue obtained by distilling off the
solvent under reduced pressure was purified by
chromatography on a silica gel column (3 to 5% methanol -
dichloromethane). Hydrochloric acid in ethanol was added
25 and the resulting mixture was concentrated. Ethyl acetate
was added to the concentrate. The colorless powder thus

obtained was collected by filtration and dried, whereby the title compound (74 mg, 21%) was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.82 (6H, s), 3.07 (4H, br), 3.30-3.90 (4H, m), 4.50 (2H, br s), 7.51 (2H, d, $J=7.8\text{Hz}$), 7.73 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.79-7.85 (2H, m), 7.86 (2H, d, $J=7.8\text{Hz}$), 8.00 (1H, br s), 8.19 (1H, d, $J=8.8\text{Hz}$), 8.25-8.30 (2H, m), 8.50 (1H, br s), 8.73 (1H, d, $J=4.9\text{Hz}$).
MS (FAB) m/z : 549 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 551 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{29}\text{H}_{29}\text{ClN}_4\text{O}_3\text{S} \cdot 1.1\text{HCl} \cdot 2\text{H}_2\text{O}$

10 Calculated: C, 55.71; H, 5.50; Cl, 11.91; N, 8.96; S, 5.13.
Found: C, 55.61; H, 5.49; Cl, 11.89; N, 9.18; S, 5.27.

[Example A-157] 1-[4-[2-[(tert-Butoxycarbonylamino)methyl]pyridin-4-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

15 In the same manner as in Referential Example 10, a reaction was effected, whereby the title compound was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (9H, s), 3.13 (4H, br), 3.40-4.00 (4H, m), 4.50 (2H, d, $J=5.4\text{Hz}$), 5.57 (1H, br s), 7.35 (1H, dd, $J=5.4, 1.5\text{Hz}$), 7.41 (2H, d, $J=8.3\text{Hz}$), 7.44 (1H, br s), 7.57-7.65 (3H, m), 7.76 (1H, dd, $J=8.3, 1.5\text{Hz}$), 7.90-7.97 (3H, m), 8.31 (1H, d, $J=1.5\text{Hz}$), 8.59 (1H, d, $J=5.4\text{Hz}$).
MS (FAB) m/z : 621 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 623 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Example A-158]

25 2-[(tert-Butoxycarbonylamino)methyl]-4-[4-[4-[(6-

chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.42 (9H, s), 3.13 (4H, br), 3.40-4.00 (4H, m), 4.52 (2H, d, $J=6.3\text{Hz}$), 5.86 (1H, br s), 7.39-7.44 (3H, m), 7.56-7.63 (4H, m), 7.77 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.91-7.97 (3H, m), 8.27 (1H, d, $J=6.8\text{Hz}$), 8.31 (1H, d, $J=2.0\text{Hz}$).

MS (FAB) m/z : 637 $[(M+H)^+, \text{Cl}^{35}]$, 639 $[(M+H)^+, \text{Cl}^{37}]$.

10 Elementary analysis for $\text{C}_{32}\text{H}_{33}\text{ClN}_4\text{O}_6\text{S}\cdot 0.7\text{H}_2\text{O}$

Calculated: C, 59.15; H, 5.34; Cl, 5.46; N, 8.62; S, 4.94.

Found: C, 58.92; H, 5.41; Cl, 5.56; N, 8.52; S, 5.05.

[Example A-159]

15 2-Aminomethyl-4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-7, the title compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.07 (4H, br), 3.35-3.95 (4H, m), 4.24 (2H, d, $J=5.4\text{Hz}$), 7.49 (2H, d, $J=8.3\text{Hz}$), 7.73 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.80-7.87 (3H, m), 7.89 (1H, dd, $J=6.8, 2.4\text{Hz}$), 8.17-8.22 (2H, m), 8.25-8.30 (2H, m), 8.45 (1H, d, $J=6.8\text{Hz}$), 8.51 (1H, br s), 8.71 (3H, br s).

MS (FAB) m/z : 537 $[(M+H)^+, \text{Cl}^{35}]$, 539 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{27}\text{H}_{25}\text{ClN}_4\text{O}_4\text{S}\cdot 1.7\text{HCl}\cdot \text{H}_2\text{O}$

25 Calculated: C, 52.56; H, 4.69; Cl, 15.51; N, 9.08; S, 5.20.

Found: C, 52.69; H, 4.85; Cl, 15.51; N, 8.90; S, 5.13.

[Example A-160] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(2-cyanopyridin-4-yl)benzoyl]piperazine

In dichloromethane (100 ml), 4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide (1.67 g) was dissolved, followed by the addition of trimethylsilylcyanide (0.42 ml) and dimethylcarbamoyl chloride (0.30 ml). The resulting mixture was stirred at room temperature for 24 hours. An aqueous solution of sodium bicarbonate and dichloromethane were added to the reaction mixture to separate the organic layer. The organic layer thus obtained was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (1% methanol - dichloromethane), whereby the title compound (1.44 g, 84%) was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.14 (4H, br s), 3.49 (2H, br s), 3.89 (2H, br s), 7.47 (2H, d, $J=8.3\text{Hz}$), 7.55-7.72 (4H, m), 7.76 (1H, dd, $J=8.8, 1.5\text{Hz}$), 7.87 (1H, s), 7.90-8.04 (3H, m), 8.31 (1H, br s), 8.77 (1H, d, $J=4.9\text{Hz}$).

MS (FAB) m/z : 517 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 519 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{27}\text{H}_{21}\text{ClN}_4\text{O}_3\text{S} \cdot 0.05\text{CH}_2\text{Cl}_2$

Calculated: C, 62.33; H, 4.08; Cl, 7.48; N, 10.75; S, 6.15.

Found: C, 62.16; H, 4.20; Cl, 7.65; N, 10.69; S, 6.04.

[Example A-161] 4-[4-[[4-[(6-Chloronaphthalen-2-

yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-cyanopyridine
N-oxide

In the same manner as in Example A-6, the title compound was obtained.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 3.13(4H, br s), 3.60(2H, br s), 3.87(2H, br s), 7.46(2H, d, $J=8.3\text{Hz}$), 7.54-7.65(4H, m), 7.76(1H, dd, $J=8.3, 1.5\text{Hz}$), 7.83(1H, d, $J=2.9\text{Hz}$), 7.90-7.97(3H, m), 8.28-8.33(2H, m).

MS (FAB) m/z : 533 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 535 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

10 Elementary analysis for $\text{C}_{27}\text{H}_{21}\text{ClN}_4\text{O}_4\text{S}$

Calculated: C, 60.84; H, 3.97; Cl, 6.65; N, 10.51; S, 6.02.

Found: C, 60.76; H, 4.04; Cl, 6.64; N, 10.39; S, 6.05.

[Example A-162] 1-[4-[2-[2-(tert-butoxycarbonylamino)ethyl]pyridin-4-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In a similar manner to Example A-3 and Example A-4, a reaction was effected using methyl 4-[2-[2-(tert-butoxycarbonylamino)ethyl]pyridin-4-yl]benzoate as a starting material, whereby the title compound was obtained.

20 $^1\text{H-NMR}$ (CDCl_3) δ : 1.42(9H, s), 3.04(2H, t, $J=6.4\text{Hz}$), 3.12(4H, br), 3.45-4.00(6H, m), 5.11(1H, br s), 7.31(1H, dd, $J=5.4, 2.0\text{Hz}$), 7.35(1H, br s), 7.41(2H, d, $J=8.3\text{Hz}$), 7.58-7.65(3H, m), 7.77(1H, dd, $J=8.3, 1.5\text{Hz}$), 7.90-7.97(3H, m), 8.31(1H, s), 8.59(1H, d, $J=5.4\text{Hz}$).

25 MS (FAB) m/z : 635 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 637 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $C_{33}H_{35}ClN_4O_5S$

Calculated: C, 62.40; H, 5.55; N, 8.82.

Found: C, 62.78; H, 5.93; N, 8.51.

[Example A-163] 4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-[2-(tert-butoxycarbonylamino)ethyl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

1H -NMR ($CDCl_3$) δ : 1.39(9H,s), 3.00-3.30(6H,m), 3.50-4.00(6H,m), 5.28(1H,br s), 7.37(1H,dd,J=6.8,2.9Hz), 7.41(2H,d,J=8.3Hz), 7.51(1H,br s), 7.56-7.63(3H,m), 7.77(1H,dd,J=8.3,1.5Hz), 7.91-7.97(3H,m), 8.28(1H,d,J=6.8Hz), 8.31(1H,d,J=1.5Hz).

MS (FAB) m/z: 651 $[(M+H)^+, Cl^{35}]$, 653 $[(M+H)^+, Cl^{37}]$.

15 Elementary analysis for $C_{33}H_{35}ClN_4O_6S \cdot 0.8H_2O$

Calculated: C, 59.55; H, 5.54; N, 8.42.

Found: C, 59.75; H, 5.61; N, 8.07.

[Example A-164] 2-(2-Aminoethyl)-4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

20 In the same manner as in Example A-7, the title compound was obtained using 4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-[2-(tert-butoxycarbonylamino)ethyl]pyridine N-oxide as a starting material.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.95-3.30 (6H,m), 3.30-3.90 (6H,m),
 7.47 (2H,d,J=8.3Hz), 7.71-8.10 (8H,m), 8.19 (1H,d,J=8.8Hz),
 8.26-8.30 (2H,m), 8.37 (1H,d,J=6.8Hz), 8.51 (1H,br s).
 MS (FAB) m/z : 551 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 553 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

5 Elementary analysis for $\text{C}_{28}\text{H}_{27}\text{ClN}_4\text{O}_4\text{S}\cdot 1.1\text{HCl}\cdot 1.6\text{H}_2\text{O}$

Calculated: C, 54.24; H, 5.09; Cl, 12.01; N, 9.04; S, 5.17.

Found: C, 54.40; H, 5.36; Cl, 11.90; N, 8.97; S, 5.27.

[Example A-165] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-5-methoxycarbonyl-1-[4-(pyridin-4-yl)benzoyl]-1,2,3,4-tetrahydropyrazine

10 In N,N -dimethylformamide (1 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-6-methoxycarbonyl-1,2,3,4-tetrahydropyrazine (60 mg) and p -nitrophenyl 4-(pyridin-4-yl)benzoate (52 mg) were dissolved, followed by the
 15 addition of sodium hydride (60% in oil, 7.20 mg) under ice cooling. The resulting mixture was stirred for 1 hour. Water and ethyl acetate were added to the reaction mixture to separate the organic layer. The organic layer was dried over anhydrous magnesium sulfate and the solvent was
 20 concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (ethyl acetate : hexane = 2:1), followed by dissolution in ethanol. To the resulting solution, 1N aqueous hydrochloric acid in ethanol was added and the resulting
 25 mixture was concentrated, whereby the title compound (58 mg, 60%) was obtained as pale yellow powder.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.51 (2H, s), 3.79 (3H, s), 3.99 (2H, s),
 7.60 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.68 (1H, br), 7.76 (2H, d, $J=7.8\text{Hz}$),
 7.90 (2H, d, $J=7.8\text{Hz}$), 7.92-7.99 (3H, m), 8.12 (2H, d, $J=5.4\text{Hz}$),
 8.16 (1H, dd, $J=8.8, 1.5\text{Hz}$), 8.58 (1H, br s), 8.93 (2H, d, $J=5.4\text{Hz}$).

5 MS (FAB) m/z : 548 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 550 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{28}\text{H}_{22}\text{ClN}_3\text{O}_5\text{S}\cdot 0.8\text{HCl}\cdot 1.3\text{H}_2\text{O}$

Calculated: C, 55.99; H, 4.26; Cl, 10.63; N, 7.00; S, 5.34.

Found: C, 55.96; H, 4.31; Cl, 10.43; N, 6.94; S, 5.56.

[Example A-166] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-5-
 10 methoxycarbonyl-4-[4-(pyridin-4-yl)benzoyl]-1,2,3,4-
 tetrahydropyrazine

In the same manner as in Referential Example 7, the
 title compound was obtained using 4-(4-bromobenzoyl)-1-[(6-
 chloronaphthalen-2-yl)sulfonyl]-5-methoxycarbonyl-1,2,3,4-
 15 tetrahydropyrazine as a starting material.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.10-3.90 (7H, m), 7.43 (1H, s),
 7.66 (2H, d, $J=8.3\text{Hz}$), 7.78 (1H, dd, $J=8.8, 2.0\text{Hz}$),
 7.96 (1H, dd, $J=8.8, 2.0\text{Hz}$), 8.02 (2H, d, $J=8.3\text{Hz}$), 8.20-
 8.38 (5H, m), 8.74 (1H, br s), 8.94 (2H, d, $J=6.3\text{Hz}$).

20 MS (FAB) m/z : 548 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 550 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{28}\text{H}_{22}\text{ClN}_3\text{O}_5\text{S}\cdot 0.8\text{HCl}\cdot 0.5\text{H}_2\text{O}$

Calculated: C, 57.37; H, 4.09; Cl, 10.89; N, 7.17; S, 5.47.

Found: C, 57.24; H, 4.15; Cl, 10.88; N, 6.97; S, 5.29.

[Example A-167] cis-1-[(6-Chloronaphthalen-2-yl)sulfonyl]-
 25 4-[4-(2-cyanopyridin-4-yl)benzoyl]-2,6-dimethylpiperazine

In the same manner as in Example A-160, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.40-1.60 (6H,m), 2.40-2.60 (2H,m), 3.40-3.90 (3H,m), 4.40-4.90 (1H,br), 7.43 (2H,d,J=8.3Hz),
 5 7.60 (1H,dd,J=8.8,2.0Hz), 7.64 (2H,d,J=8.3Hz),
 7.69 (1H,dd,J=5.4,2.0Hz), 7.76 (1H,dd,J=8.8,1.5Hz),
 7.88 (1H,d,J=2.0Hz), 7.90-7.95 (3H,m), 8.31 (1H,d,J=1.5Hz),
 8.78 (1H,d,J=5.4Hz).

MS (FAB) m/z: 545 [(M+H)⁺, Cl³⁵], 547 [(M+H)⁺, Cl³⁷].

10 Elementary analysis for C₂₉H₂₅ClN₄O₃S

Calculated: C, 63.90; H, 4.62; Cl, 6.50; N, 10.28; S, 5.88.

Found: C, 63.87; H, 4.98; Cl, 6.33; N, 9.96; S, 5.75.

[Example A-168] 4-[4-[[cis-4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2,6-dimethylpiperazin-1-yl]carbonyl]phenyl]-2-
 15 cyanopyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.42-1.55 (6H,m), 2.43-2.60 (2H,m), 3.40-3.90 (3H,m), 4.40-4.90 (1H,br), 7.42 (2H,d,J=8.3Hz),
 20 7.58 (2H,d,J=8.3Hz), 7.60-7.65 (2H,m),
 7.76 (1H,dd,J=8.8,2.0Hz), 7.83 (1H,d,J=2.9Hz), 7.90-7.95 (3H,m), 8.29-8.32 (2H,m).

MS (FAB) m/z: 561 [(M+H)⁺, Cl³⁵], 563 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₉H₂₅ClN₄O₄S·0.3H₂O

25 Calculated: C, 61.49; H, 4.56; Cl, 6.26; N, 9.89; S, 5.66.

Found: C, 61.47; H, 4.63; Cl, 6.13; N, 9.72; S, 5.73.

[Example A-169] 1-[4-[(3-Aminomethyl)phenyl]benzoyl]-4-
[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example A-4 and Example A-7,
5 a reaction was effected, whereby the title compound was
obtained.

¹H-NMR (DMSO-d₆) δ: 3.07(4H,br), 3.51(2H,br), 3.69(2H,br),
4.09(2H,s), 7.45(2H,d,J=8.3Hz), 7.47-7.55(2H,m), 7.66-
7.76(4H,m), 7.80-7.87(2H,m), 8.19(2H,d,J=8.8Hz), 8.25-
10 8.42(4H,m), 8.51(1H,br s).

MS (FAB) m/z: 520 [(M+H)⁺, Cl³⁵], 522 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₈H₂₆ClN₃O₃S·HCl

Calculated: C, 60.34; H, 4.89; Cl, 12.74; N, 7.55; S, 5.76.

Found: C, 60.15; H, 4.89; Cl, 12.44; N, 7.52; S, 5.80.

15 [Example A-170] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
[[2,5-dihydro-5-oxo-3-(pyridin-4-yl)-1,2,4-triazin-6-
yl]carbonyl]piperazine

In the same manner as in Example A-4, the title
compound was obtained.

20 ¹H-NMR (DMSO-d₆) δ: 2.94(2H,br s), 3.07(2H,br s),
3.52(2H,br s), 3.73(2H,br s), 7.74(1H,dd,J=8.8,2.4Hz),
7.84(1H,dd,J=8.8,2.0Hz), 7.99(2H,d,J=6.3Hz),
8.20(1H,d,J=8.8Hz), 8.26-8.31(2H,m), 8.53(1H,br s),
8.87(2H,d,J=6.3Hz).

25 MS (FAB) m/z: 511 [(M+H)⁺, Cl³⁵], 513 [(M+H)⁺, Cl³⁷].

Elementary analysis for $C_{23}H_{19}ClN_6O_4S \cdot 0.6HCl \cdot 1.5H_2O$

Calculated: C, 49.34; H, 4.07; Cl, 10.13; N, 15.01; S, 5.73.

Found: C, 49.25; H, 4.01; Cl, 10.12; N, 15.07; S, 5.59.

[Example A-171] trans-2,6-Bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example A-105, the title compound was obtained as colorless amorphous powder by using trans-2,6-bis(methoxycarbonylmethyl)-1-(4-bromobenzoyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

1H -NMR (DMSO- d_6) δ : 2.50-2.65 (2H, m), 3.70-3.80 (2H, m), 3.30-3.40 (4H, m), 3.46 (6H, s), 4.23 (2H, br), 7.60 (2H, d, $J=8.3$ Hz), 7.74 (1H, d, $J=8.8$ Hz), 7.85 (1H, d, $J=8.3$ Hz), 8.03 (2H, d, $J=8.3$ Hz), 8.15-8.40 (4H, m), 8.53 (1H, s), 8.90-9.00 (2H, m).

MS (FAB) m/z : 636 $[(M+H)^+, Cl^{35}]$, 638 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{32}H_{30}ClN_3O_7S \cdot HCl \cdot 2.6H_2O$

Calculated: C, 53.42; H, 5.07; Cl, 9.86; N, 5.84; S, 4.46.

Found: C, 53.21; H, 4.75; Cl, 9.91; N, 5.80; S, 4.54.

[Example A-172] cis-2,6-Bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example A-171, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.70-3.00 (6H,m), 3.40-3.80 (2H,m),
 3.51 (3H,s), 3.68 (3H,s), 4.13 (1H,br), 4.97 (1H,br),
 7.58 (2H,d,J=7.8Hz), 7.70-7.75 (1H,m), 7.80-7.90 (1H,m),
 8.03 (2H,d,J=8.3Hz), 8.19 (1H,d,J=8.8Hz), 8.25-8.35 (4H,m),
 8.55 (1H,s), 8.90-8.95 (2H,m).

MS (FAB) m/z: 636 [(M+H)⁺, Cl³⁵], 638 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₃₂H₃₀ClN₃O₇S·HCl·0.3H₂O

Calculated: C, 56.69; H, 4.70; Cl, 10.46; N, 6.20; S, 4.73.

Found: C, 56.72; H, 4.66; Cl, 10.31; N, 6.03; S, 4.71.

[Example A-173] cis-2,6-Bis(carbamoylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example A-35, the title compound was obtained using cis-2,6-

bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine as a starting material.

¹H-NMR (DMSO-d₆) δ: 2.30-2.60 (10H,m), 2.80-2.90 (2H,m),
 3.45-3.55 (1H,m), 3.75-3.85 (1H,m), 4.10-4.20 (1H,m), 4.95-
 5.05 (1H,m), 6.85 (1H,br s), 7.03 (1H,br s), 7.40 (1H,br s),
 7.45 (1H,br s), 7.56 (2H,d,J=8.3Hz), 7.70-7.75 (1H,m), 7.80-
 7.85 (1H,m), 8.02 (2H,d,J=8.3Hz), 8.18 (1H,d,J=8.8Hz), 8.25-
 8.40 (4H,m), 8.52 (1H,s), 8.95 (2H,d,J=6.8Hz).

MS (FAB) m/z: 606 [(M+H)⁺, Cl³⁵], 608 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₃₀H₂₈ClN₅O₅S·1.2HCl·2.8H₂O

Calculated: C, 51.45; H, 5.01; N, 11.14; Cl, 10.00; S, 4.58.

Found: C, 51.52; H, 5.30; N, 11.33; Cl, 10.01; S, 4.72.

5 [Example A-174] 4-[4-[[cis-2,6-Bis(carbamoylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

10 ¹H-NMR (DMSO-d₆) δ: 2.30-2.60 (4H,m), 2.75-2.90 (2H,m), 3.45-3.55 (1H,m), 3.75-3.85 (1H,m), 4.10-4.20 (1H,m), 4.90-5.00 (1H,m), 6.86 (1H,br), 7.02 (1H,br), 7.30-7.50 (4H,m), 7.70-7.85 (6H,m), 8.18 (1H,d,J=8.8Hz), 8.25-8.35 (4H,m), 8.52 (1H,s).

15 MS (FAB) m/z: 622 [(M+H)⁺, Cl³⁵], 624 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₃₀H₂₈ClN₅O₆S·1.6H₂O

Calculated: C, 55.36; H, 4.83; Cl, 5.45; N, 10.76; S, 4.93.

Found: C, 55.05; H, 4.77; Cl, 5.77; N, 10.51; S, 4.90.

20 [Example A-175] 4-[4-[[cis-2,6-Bis(ethoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

25 ¹H-NMR (CDCl₃) δ: 2.85-2.95 (4H,m), 3.20-3.40 (4H,m), 3.63 (6H,s), 4.25-4.35 (2H,m), 7.45-7.50 (4H,m), 7.55-

7.65 (3H,m), 7.70-7.80 (1H,m), 7.90-7.95 (3H,m), 8.25-8.35 (3H,m).

MS (FAB) m/z: 652 [(M+H)⁺, Cl³⁵], 654 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₃₂H₃₀ClN₃O₈S·2.3H₂O

5 Calculated: C, 55.42; H, 5.03; Cl, 5.11; N, 6.06; S, 4.62.

Found: C, 55.50; H, 4.93; Cl, 5.12; N, 5.89; S, 4.54.

[Example A-176] trans-2,6-Bis(carbamoylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

10 In the same manner as in Example A-105, the title compound was obtained using trans-2,6-bis(carbamoylmethyl)-1-(4-bromobenzoyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

¹H-NMR (DMSO-d₆) δ: 2.50-2.60 (4H,m), 3.20-3.30 (4H,m), 4.15-4.25 (2H,m), 6.87 (2H,br s), 7.40 (2H,br s), 7.62 (2H,d,J=8.8Hz), 7.72 (1H,d,J=8.3Hz), 7.82 (1H,d,J=8.8Hz), 8.02 (2H,d,J=8.3Hz), 8.16 (1H,d,J=8.8Hz), 8.20-8.40 (4H,m), 8.51 (1H,s), 8.90-9.00 (2H,m).

MS (FAB) m/z: 606 [(M+H)⁺, Cl³⁵], 608 [(M+H)⁺, Cl³⁷].

20 Elementary analysis for C₃₀H₂₈ClN₅O₅S·1.2HCl·3H₂O

Calculated: C, 51.19; H, 5.04; Cl, 11.08; N, 9.95; S, 4.56.

Found: C, 51.10; H, 4.97; Cl, 11.17; N, 9.71; S, 4.64.

[Example A-177] 4-[4-[[trans-2,6-Bis(carbamoylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

25

In the same manner as in Example A-6, the title

compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.55-2.65 (2H,m), 2.65-2.80 (2H,m), 3.20-3.60 (4H,m), 4.25-4.35 (2H,m), 4.90-5.00 (1H,m), 6.98 (2H,br), 7.48 (2H,br), 7.55-7.65 (2H,m), 7.80-8.00 (6H,m), 8.20-8.40 (5H,m), 8.60 (1H,s).

MS (FAB) m/z : 622 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 624 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Example A-178] *trans*-2,6-bis(carboxymethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

10 In the same manner as in Example A-3, the title compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.50-2.75 (4H,m), 3.25-3.45 (4H,m), 4.15-4.25 (2H,m), 7.52 (2H,d, $J=8.3\text{Hz}$), 7.70-7.75 (3H,m), 7.80-7.85 (3H,m), 8.16 (1H,d, $J=8.8\text{Hz}$), 8.20-8.30 (2H,m), 8.51 (1H,s), 8.60-8.70 (2H,m), 12.32 (2H,s).

MS (FAB) m/z : 608 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 610 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{30}\text{H}_{26}\text{ClN}_3\text{O}_7\text{S}\cdot 0.2\text{HCl}\cdot 0.5\text{H}_2\text{O}$

Calculated: C, 57.71; H, 4.39; Cl, 6.81; N, 6.73; S, 5.14.

Found: C, 57.78; H, 4.35; Cl, 6.73; N, 6.68; S, 5.11.

20 [Example A-179] *trans*-2,6-Bis(2-hydroxyethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

In tetrahydrofuran (40 ml), *trans*-2,6-bis(carboxymethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine (269 mg) was suspended,

25

followed by the addition of N,N-diisopropylethylamine (480
µl) and 1-benzotriazolyloxy-tris(pyrrolidino)phosphonium
hexafluorophosphate (672 mg) under ice cooling. The
resulting mixture was stirred for 3.5 hours at room
5 temperature. Under ice cooling, sodium borohydride (297
mg) was added and the resulting mixture was stirred for 15
hours at room temperature. The reaction mixture was ice
cooled and added with water and ethyl acetate to separate
the organic layer. The organic layer thus obtained was
10 washed with aqueous NaCl solution, dried over anhydrous
sodium sulfate. The residue obtained by distilling off the
solvent under reduced pressure was purified by
chromatography on a silica gel column (4% methanol -
dichloromethane), followed by dissolution in
15 tetrahydrofuran. Saturated hydrochloride in methanol was
added to the resulting solution and the resulting mixture
was concentrated to dryness. Ethyl acetate was then added
to the residue to crystallize the same, whereby the title
compound was obtained.

20 $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.60-1.80 (2H,m), 1.80-1.95 (2H,m), 3.20-
3.40 (6H,m), 3.95-4.05 (2H,m), 7.59 (2H,d,J=8.3Hz), 7.70-
7.75 (3H,m), 7.80-7.90 (31H,m), 7.99 (2H,d,J=8.3Hz),
8.17 (1H,d,J=8.8Hz), 8.20-8.30 (4H,m), 8.54 (1H,s), 8.85-
8.95 (2H,m).

25 HRMS (FAB) m/z : 580.1633 ($\text{M}+\text{H}$) $^+$ (calcd for $\text{C}_{30}\text{H}_{30}\text{ClN}_3\text{O}_5\text{S}$
580.1673).

[Example A-180] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[4-(2-methylpyridin-4-yl)benzoyl]piperazine

In the same manner as in Example A-4, the title compound was obtained.

5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 2.74 (3H, s), 2.99-3.81 (8H, br),
7.71 (1H, s), 7.33 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.51 (1H, d, $J=8.8\text{Hz}$),
7.58 (2H, d, $J=8.3\text{Hz}$), 7.79 (1H, d, $J=2.0\text{Hz}$), 8.00 (2H, d, $J=8.3\text{Hz}$),
8.77-8.84 (1H, m), 8.79 (1H, d, $J=6.3\text{Hz}$), 12.50 (1H, s).
MS (FAB) m/z : 495 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 497 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

10 Elementary analysis for $\text{C}_{25}\text{H}_{23}\text{ClN}_4\text{O}_3\text{S}\cdot 0.9\text{HCl}\cdot \text{H}_2\text{O}$
Calculated: C, 55.01; H, 4.78; Cl, 12.34; N, 10.26; S,
5.87.
Found: C, 54.99; H, 5.01; Cl, 12.12; N, 10.03; S,
5.88.

15 [Example A-181] 4-[4-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-methylpyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

20 MS (FAB) m/z : 511 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 513 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.
 $^1\text{H-NMR}$ (DMSO-d_6) δ : 2.95-3.18 (4H, br), 3.37-3.81 (4H, br),
7.03 (1H, s), 7.34 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.47 (2H, d, $J=8.3\text{Hz}$),
7.51 (1H, d, $J=8.8\text{Hz}$), 7.66 (1H, dd, $J=6.8, 2.9\text{Hz}$), 7.79 (1H, s),
7.80 (2H, d, $J=8.3\text{Hz}$), 7.91 (1H, d, $J=2.9\text{Hz}$), 8.30 (1H, d, $J=6.8\text{Hz}$),
25 12.42 (1H, s).

Elementary analysis for $C_{25}H_{23}ClN_4O_4S \cdot 0.8H_2O$

Calculated: C, 57.15; H, 4.72; Cl, 6.75; N, 10.66; S, 6.10.

Found: C, 57.22; H, 4.64; Cl, 7.04; N, 10.42; S, 6.17.

[Example A-182] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

At room temperature, 1-[(5-bromopyrimidin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine (500 mg) and (pyridin-2-yl)tributyltin (418 mg) were dissolved in N,N-dimethylformamide (10 ml). To the reaction mixture was added tetrakis(triphenylphosphine)palladium(0) (69 mg), followed by stirring at 100°C for 9 hours. After cooling to room temperature, ethyl acetate and ammonia solution were added. The resulting mixture was separated by ethyl acetate and water. The organic layer was dried over anhydrous sodium sulfate. The filtrate was concentrated and the residue was purified by chromatography on a silica gel column (4% methanol - methylene chloride). The resulting fraction was added with ethanol, followed by concentration. Diethyl ether was then added to the concentrate. Colorless powder thus precipitated was collected by filtration and dried, whereby the free form (254 mg) of the title compound was obtained. The resulting free form was dissolved in methylene chloride, followed by the addition of 1N hydrochloric acid (in ethanol) to make the solution acidic. After concentration, ethyl acetate and diethyl ether were

added, followed by concentration. Colorless powder thus precipitated was collected by filtration and dried, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.90-2.98 (2H,m), 3.10-3.15 (2H,m), 3.30-3.41 (2H,m), 3.75-3.85 (2H,m), 7.05 (1H,d,J=2.0Hz), 7.35 (1H,dd,J=2.0 and 8.8Hz), 7.47-7.53 (2H,m), 7.80 (1H,d,J=2.0Hz), 8.00 (1H,dt,J=2.0 and 8.3Hz), 8.17 (1H,d,J=8.3Hz), 8.76 (1H,d,J=4.4Hz), 9.47 (2H,s), 12.47 (1H,s).

MS (FAB) m/z: 483 [(M+H)⁺, Cl³⁵], 485 [(M+H)⁺, Cl³⁷].

[Example A-183] 2-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 3.10-3.20 (2H,m), 3.20-3.30 (2H,m), 3.50-3.60 (2H,m), 3.85-3.95 (2H,m), 6.97 (1H,s), 7.30-7.52 (5H,m), 7.68 (1H,s), 8.39 (1H,d,J=5.9Hz), 9.28 (2H,s), 9.50 (1H,s).

MS (FAB) m/z: 499 [(M+H)⁺, Cl³⁵], 501 [(M+H)⁺, Cl³⁷].

[Example A-184] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.01-3.10 (2H,m), 3.17-3.26 (2H,m), 3.39-3.47 (2H,m), 3.79-3.87 (2H,m), 7.52 (1H,dd,J=7.3 and 4.9Hz),

7.61 (1H, d, J=8.8Hz), 8.01 (1H, dt, J=1.5 and 7.3Hz),
 8.10 (1H, d, J=8.8Hz), 8.12 (1H, s), 8.18 (1H, d, J=7.3Hz),
 8.35 (1H, s), 8.76 (1H, d, J=4.9Hz), 9.48 (2H, s).
 MS (FAB) m/z: 500 [(M+H)⁺, Cl³⁵], 502 [(M+H)⁺, Cl³⁷].

5 [Example A-185] 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

10 ¹H-NMR (CDCl₃) δ: 3.24 (2H, t, J=4.9Hz), 3.33 (2H, t, J=4.9Hz),
 3.63 (2H, t, J=4.9Hz), 3.99 (2H, t, J=4.9Hz), 7.36-7.53 (4H, m),
 7.78 (1H, s), 7.84 (1H, d, J=8.3Hz), 7.88 (1H, br s), 8.36-
 8.39 (1H, m), 9.29 (2H, s).

MS (FAB) m/z: 516 [(M+H)⁺, Cl³⁵], 518 [(M+H)⁺, Cl³⁷].

15 [Example A-186] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(2-methylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

20 ¹H-NMR (DMSO-d₆) δ: 2.71 (3H, s), 2.96 (2H, br s), 3.16 (2H, br
 s), 3.30 (2H, br s), 3.81 (2H, br s), 7.05 (1H, s),
 7.35 (1H, d, J=8.8Hz), 7.51 (1H, d, J=8.8Hz), 7.81 (1H, s),
 8.13 (1H, br s), 8.23 (1H, br s), 8.84 (1H, br s), 9.40 (2H, s),
 12.50 (1H, s).

MS (FAB) m/z: 497 [(M+H)⁺, Cl³⁵], 499 [(M+H)⁺, Cl³⁷].

25 [Example A-187] 4-[2-[[4-[(5-Chloroindol-2-

yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-methylpyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

5 ^1H -NMR (DMSO- d_6) δ : 2.77(3H,s), 3.16-3.20(2H,m), 3.28-3.31(2H,m), 3.57-3.60(2H,m), 3.95-3.98(2H,m), 6.97(1H,d,J=1.5Hz), 7.32-7.42(3H,m), 7.50(1H,d,J=2.9Hz), 7.69(1H,s), 8.39(1H,d,J=6.8Hz), 8.92-9.05(3H,m).

MS (FAB) m/z : 513 [(M+H) $^+$, Cl 35], 515 [(M+H) $^+$, Cl 37].

10 [Example A-188] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(2-methylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

15 ^1H -NMR (DMSO- d_6) δ : 2.74(3H,s), 3.01-3.09(2H,m), 3.17-3.25(2H,m), 3.38-3.45(2H,m), 3.80-3.90(2H,m), 7.61(1H,dd,J=8.8,2.0Hz), 8.10(1H,d,J=8.8Hz), 8.13(1H,s), 8.20(1H,d,J=5.9Hz), 8.31(1H,br s), 8.36(1H,d,J=2.0Hz), 8.87(1H,d,J=5.9Hz), 9.43(2H,s).

20 MS (FAB) m/z : 514 [(M+H) $^+$, Cl 35], 516 [(M+H) $^+$, Cl 37].

[Example A-189] 4-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-methylpyridine N-oxide

25 In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.60 (3H, s), 3.24 (2H, br), 3.34 (2H, br),
 3.60 (2H, br), 3.99 (2H, br), 7.39 (1H, dd, J=2.4 and 6.8 Hz),
 7.47 (1H, dd, J=1.5 and 8.8 Hz), 7.50 (1H, d, J=2.4 Hz),
 7.78 (1H, s), 7.83 (1H, d, J=8.8 Hz), 7.88 (1H, d, J=1.5 Hz),
 8.38 (1H, d, J=6.8 Hz), 8.99 (2H, s).

MS (FAB) m/z: 530 [(M+H)⁺, Cl³⁵], 532 [(M+H)⁺, Cl³⁷].

[Example A-190] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-
 4-[[5-(3-fluoropyridin-4-yl)pyrimidin-2-
 yl]carbonyl]piperazine

10 In the same manner as in Example A-182, the title
 compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.06 (2H, br s), 3.21 (2H, br s),
 3.44 (2H, br s), 3.84 (2H, br s), 7.60 (1H, dd, J=8.8, 2.0 Hz),
 7.84 (1H, dd, J=6.4, 4.9 Hz), 8.09 (1H, d, J=8.8 Hz), 8.12 (1H, s),
 8.35 (1H, d, J=2.0 Hz), 8.62 (1H, d, J=4.9 Hz), 8.79 (1H, d, J=2.0 Hz),
 9.20 (2H, s).

MS (FAB) m/z: 518 [(M+H)⁺, Cl³⁵], 520 [(M+H)⁺, Cl³⁷].

[Example A-191] 4-[2-[[4-[(6-Chlorobenzo[b]thien-2-
 yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-3-
 20 fluoropyridine N-oxide

In the same manner as in Example A-6, the title
 compound was obtained.

¹H-NMR (CDCl₃) δ: 3.23-3.27 (2H, m), 3.32-3.36 (2H, m), 3.59-
 3.63 (2H, m), 3.98-4.01 (2H, m), 7.36-7.43 (1H, m),
 7.47 (1H, d, J=8.3 Hz), 7.78 (1H, s), 7.83 (1H, d, J=8.3 Hz),

7.88 (1H, s), 8.18 (1H, d, J=6.8 Hz), 8.30 (1H, d, J=5.9 Hz),
9.00 (2H, s).

HRMS (FAB) m/z: 534.0468 [(M+H)⁺ calcd for C₂₂H₁₈ClFN₅O₄S₂,
534.0473].

5 [Example A-192]

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(2,6-
dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title
compound was obtained.

10 ¹H-NMR (DMSO-d₆) δ: 2.71 (6H, s), 2.95 (2H, br s), 3.16 (2H, br
s), 3.37 (2H, br s), 3.81 (2H, br s), 7.05 (1H, s),
7.35 (1H, dd, J=8.8, 2.0 Hz), 7.51 (1H, d, J=8.8 Hz), 7.80 (1H, br s),
8.14 (2H, br s), 9.39 (2H, s), 12.50 (1H, s).
MS (FAB) m/z: 511 [(M+H)⁺, Cl³⁵], 513 [(M+H)⁺, Cl³⁷].

15 [Example A-193] 4-[2-[[4-[(5-Chloroindol-2-
yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,6-
dimethylpyridine N-oxide

In the same manner as in Example A-6, the title
compound was obtained.

20 ¹H-NMR (CDCl₃) δ: 2.61 (6H, s), 3.18 (2H, d, J=4.9 Hz),
3.29 (2H, d, J=4.9 Hz), 3.59 (2H, d, J=4.9 Hz), 3.97 (2H, d, J=4.9 Hz),
6.97 (1H, d, J=1.5 Hz), 7.35 (1H, dd, J=8.8 and 2.0 Hz), 7.38-
7.43 (3H, m), 7.69 (1H, d, J=2.0 Hz), 8.89 (1H, br s), 8.98 (2H, s).
MS (FAB) m/z: 527 [(M+H)⁺, Cl³⁵], 529 [(M+H)⁺, Cl³⁷].

25 [Example A-194] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-

(2,5-dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 2.39(3H,s), 2.68(3H,s), 2.97(2H,br s), 3.16(2H,br s), 3.40(2H,br s), 3.81(2H,br s), 7.06(1H,s), 7.34(1H,dd, $J=8.8$ and 2.0Hz), 7.52(1H,d, $J=8.8\text{Hz}$), 7.79-7.83(2H,m), 8.76(1H,s), 9.32(2H,s), 12.52(1H,s).

MS (FAB) m/z : 511 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 513 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

10 [Example A-195] 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,5-dimethylpyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

15 $^1\text{H-NMR}$ (CDCl_3) δ : 2.25(3H,s), 2.54(3H,s), 3.15-3.25(2H,m), 3.25-3.38(2H,m), 3.55-3.65(2H,m), 3.90-4.05(2H,m), 6.97(1H,s), 7.13(1H,s), 7.34(1H,dd, $J=8.8$ and 1.5Hz), 7.41(1H,d, $J=8.8\text{Hz}$), 7.68(1H,d, $J=1.5\text{Hz}$), 8.28(1H,s), 8.78(2H,s), 9.20(1H,s).

20 MS (FAB) m/z : 527 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 529 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Example A-196] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(2,3-dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

25 In the same manner as in Example A-182, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.33(3H,s), 2.76(3H,s), 2.97(2H,br s),
3.17(2H,br s), 3.43(2H,br s), 3.82(2H,br s), 7.06(1H,s),
7.34(1H,dd,J=8.8 and 2.0Hz), 7.52(1H,d,J=8.8Hz), 7.78-
7.85(2H,m), 8.72(1H,d,J=5.9Hz), 9.01(2H,s), 12.52(1H,s).

5 MS (FAB) m/z: 511 [(M+H)⁺, Cl³⁵], 513 [(M+H)⁺, Cl³⁷].

[Example A-197] 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,3-dimethylpyridine N-oxide

10 In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.27(3H,s), 2.61(3H,s),
3.20(2H,t,J=4.9Hz), 3.31(2H,t,J=4.9Hz), 3.62(2H,t,J=4.9Hz),
3.98(2H,t,J=4.9Hz), 6.97(1H,d,J=1.5Hz), 7.00(1H,d,J=6.8Hz),
7.35(1H,dd,J=8.8 and 2.0Hz), 7.40(1H,d,J=8.8Hz),
15 7.68(1H,d,J=2.0Hz), 8.29(1H,d,J=6.8Hz), 8.75(2H,s),
9.02(1H,s).

MS (FAB) m/z: 527 [(M+H)⁺, Cl³⁵], 529 [(M+H)⁺, Cl³⁷].

[Example A-198] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl-4-
[[5-(2,3-dimethylpyridin-4-yl)pyridimin-2-yl]carbonyl]piperazine
20

In the same manner as in Example A-182, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.31(3H,s), 2.73(3H,s), 3.05(2H,br s),
3.21(2H,br s), 3.46(2H,br s), 3.84(2H,br s),
25 7.59(1H,dd,J=8.5,2.0Hz), 7.78(1H,d,J=5.4Hz),

8.08 (1H, d, J=8.5Hz), 8.12 (1H, s), 8.34 (1H, d, J=2.0Hz),
8.70 (1H, d, J=5.4Hz), 9.00 (2H, s).

MS (FAB) m/z: 528 [(M+H)⁺, Cl³⁵], 530 [(M+H)⁺, Cl³⁷].

[Example A-199] 4-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,3-dimethylpyridine N-oxide

In the same manner as in Example A-182, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.28 (3H, s), 2.60 (3H, s),
10 3.26 (2H, d, J=4.9Hz), 3.35 (2H, d, J=4.9Hz), 3.64 (2H, d, J=4.9Hz),
4.00 (2H, d, J=4.9Hz), 7.01 (1H, d, J=6.6Hz), 7.47 (1H, dd, J=1.7
and 8.8Hz), 7.78 (1H, s), 7.83 (1H, d, J=8.8Hz),
7.88 (1H, d, J=1.7Hz), 8.28 (1H, d, J=6.6Hz), 8.76 (2H, s).

MS (FAB) m/z: 544 [(M+H)⁺, Cl³⁵], 546 [(M+H)⁺, Cl³⁷].

15 [Example A-200] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(3,5-dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

20 ¹H-NMR (DMSO-d₆) δ: 2.16 (6H, s), 2.99 (2H, br s), 3.17 (2H, br
s), 3.42 (2H, br s), 3.82 (2H, br s), 7.06 (1H, s),
7.34 (1H, d, J=8.8Hz), 7.51 (1H, d, J=8.8Hz), 7.80 (1H, s),
8.72 (2H, br s), 8.91 (2H, s), 12.50 (1H, s).

MS (FAB) m/z: 511 [(M+H)⁺, Cl³⁵], 513 [(M+H)⁺, Cl³⁷].

25 [Example A-201] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(6-

methyipyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.57(3H,s), 2.96(2H,br s), 3.15(2H,br
5 s), 3.36(2H,br s), 3.80(2H,br s), 7.05(1H,d,J=2.0Hz),
7.35(1H,dd,J=8.8,2.0Hz), 7.38(1H,d,J=7.3Hz),
7.51(1H,d,J=8.8Hz), 7.81(1H,d,J=2.0Hz), 7.89(1H,t,J=7.3Hz),
7.96(1H,d,J=7.3Hz), 9.44(2H,s), 12.49(1H,s).

MS (FAB) m/z: 497 [(M+H)⁺, Cl³⁵], 499 [(M+H)⁺, Cl³⁷].

10 [Example A-202] 2-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-6-methyipyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

15 ¹H-NMR (CDCl₃) δ: 2.59(3H,s), 3.15(2H,d,J=4.9Hz),
3.26(2H,d,J=4.9Hz), 3.56(2H,d,J=4.9Hz), 3.94(2H,d,J=4.9Hz),
6.97(1H,s), 7.30-7.41(5H,m), 7.69(1H,s), 9.07(1H,s),
9.25(2H,s).

MS (FAB) m/z: 513 [(M+H)⁺, Cl³⁵], 515 [(M+H)⁺, Cl³⁷].

20 [Example A-203] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(3-methyipyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.41(3H,s), 2.97(2H,br s), 3.16(2H,br
25 s), 3.40(2H,br s), 3.80(2H,br s), 7.05(1H,s),

7.33 (1H, dd, J=8.8, 2.0Hz), 7.50 (1H, d, J=8.8Hz),
 7.79 (1H, d, J=2.0Hz), 7.84 (1H, d, J=5.4Hz), 8.79 (1H, d, J=5.4Hz),
 8.85 (1H, s), 9.04 (2H, s), 12.49 (1H, s).

MS (FAB) m/z: 497 [(M+H)⁺, Cl³⁵], 499 [(M+H)⁺, Cl³⁷].

5 [Example A-204] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(5-methylpyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.37 (3H, s), 2.94-2.97 (2H, m), 3.13-
 10 3.16 (2H, m), 3.35-3.39 (2H, m), 3.78-3.81 (2H, m),
 7.05 (1H, d, J=2.0Hz), 7.34 (1H, dd, J=8.8, 2.0Hz),
 7.51 (1H, d, J=8.8Hz), 7.78-7.83 (2H, m), 8.07 (1H, d, J=8.3Hz),
 8.60 (1H, d, J=1.5Hz), 9.44 (2H, s), 12.47 (1H, s).

MS (FAB) m/z: 497 [(M+H)⁺, Cl³⁵], 499 [(M+H)⁺, Cl³⁷].

15 [Example A-205] 2-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-5-methylpyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

20 ¹H-NMR (CDCl₃) δ: 2.40 (3H, s), 3.16-3.19 (2H, m), 3.26-
 3.29 (2H, m), 3.58-3.61 (2H, m), 3.95-3.98 (2H, m), 6.98 (1H, s),
 7.20-7.41 (4H, m), 7.70 (1H, s), 8.24 (1H, s), 9.04 (1H, s),
 9.27 (2H, s).

MS (FAB) m/z: 513 [(M+H)⁺, Cl³⁵], 515 [(M+H)⁺, Cl³⁷].

25 HRMS (FAB) m/z: 513.1144 (M+H)⁺ (calcd for C₂₃H₂₂ClN₆O₄S,

513.1112).

[Example A-206] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(3-methylpyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title
5 compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.41(3H,s), 2.98(2H,br s), 3.15(2H,br
s), 3.40(2H,br s), 3.81(2H,br s), 7.05(1H,s),
7.34(1H,dd,J=8.8,2.0Hz), 7.45(1H,dd,J=7.8,4.9Hz),
7.51(1H,d,J=8.8Hz), 7.80(1H,s), 7.85(1H,d,J=7.8Hz),
10 8.59(1H,d,J=4.9Hz), 9.09(2H,s), 12.49(1H,s).

MS (FAB) m/z: 497 [(M+H)⁺, Cl³⁵], 499 [(M+H)⁺, Cl³⁷].

[Example A-207] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]thiocarbonyl]piperazine

In a mixed solvent of dimethoxyethane (10 ml) and
15 toluene (10 ml) was suspended 1-[(5-chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine (100 mg) at room temperature,
followed by the addition of Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide,
20 42 mg). The resulting mixture was heated under reflux for 2 days. After cooling to room temperature, the reaction mixture was concentrated and the residue was purified by chromatography on a silica gel column (3 → 5% methanol - methylene chloride). 1N hydrochloric acid (in ethanol) was
25 added to make acidic the purified product. After concentration, ethyl acetate was added. Yellow powder so

precipitated was collected by filtration and dried, whereby the title compound (34 mg) was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.00(3H, br s), 3.28(2H, br s), 3.59(2H, br s), 4.44(2H, br s), 7.06(1H, s), 7.34(1H, dd, $J=9.0, 2.0\text{Hz}$), 7.51(1H, d, $J=9.0\text{Hz}$), 7.80(1H, d, $J=2.0\text{Hz}$), 8.21(2H, d, $J=6.1\text{Hz}$), 8.90(2H, d, $J=6.1\text{Hz}$), 9.33(2H, s), 12.51(1H, s).

MS (FAB) m/z : 499 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 501 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Example A-208] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(hydroxyimino)[5-(pyridin-4-yl)pyrimidin-2-yl]methyl]piperazine

In ethanol (50 ml) was suspended 1-[(5-chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]thiocarbonyl]piperazine (243 mg) at room temperature, followed by the successive addition of hydroxylamine hydrochloride (338 mg), sodium acetate (399 mg) and mercury (II) chloride (132 mg). The resulting mixture was stirred at room temperature for 6 hours. The insoluble matter was filtered off through Celite filtration. The residue was purified by chromatography on a silica gel column (7% methanol - methylene chloride), whereby two fractions were obtained. They were concentrated, respectively, whereby a low-polarity compound (20 mg, colorless powder) and a high-polarity compound (20 mg, colorless powder) were obtained.

Low-polarity compound:

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.01(4H, br s), 3.09(4H, br s),

7.00 (1H, s), 7.25-7.35 (1H, m), 7.49 (1H, d, J=9.0 Hz), 7.78 (1H, br s), 7.89 (2H, d, J=6.1 Hz), 8.73 (2H, d, J=6.1 Hz), 9.30 (2H, s).

HRMS (FAB) m/z: 498.1115 (M+H)⁺ (calcd for C₂₂H₂₁ClN₇O₃S, 498.1115).

5 High-polarity compound:

¹H-NMR (DMSO-d₆) δ: 3.06 (4H, br s), 3.30-3.32 (4H, unclear because of the overlapping with that of water), 7.03 (1H, s), 7.33 (1H, d, J=8.8 Hz), 7.51 (1H, d, J=8.8 Hz), 7.80 (1H, br s), 7.87 (2H, d, J=6.1 Hz), 8.73 (2H, d, J=6.1 Hz), 9.24 (2H, s).

10 HRMS (FAB) m/z: 498.1110 (M+H)⁺ (calcd for C₂₂H₂₁ClN₇O₃S, 498.1115).

[Example A-209] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(hydrazono)[5-(pyridin-4-yl)pyrimidin-2-yl]methyl]piperazine

15 In a mixed solvent of ethanol (100 ml) and methylene chloride (100 ml) was suspended 1-[(5-chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]thiocarbonyl]piperazine (499 mg) at room temperature, followed by the successive addition of hydrazine
20 monohydrate (146 µg) and mercury (II) chloride (272 mg). The resulting mixture was stirred at room temperature for 4 hours. After the solvent was distilled off, the residue was purified by chromatography on a silica gel column (8% methanol - methylene chloride). Methylene chloride was
25 added and the resulting mixture was concentrated. Yellow crystals thus precipitated were collected by filtration and

dried, whereby the title compound (100 mg) was obtained.

¹H-NMR (DMSO-d₆) δ: 3.03(8H, br s), 6.77(2H, br s),
7.04(1H, s), 7.34(1H, dd, J=8.8 and 2.0Hz),
7.52(1H, d, J=8.8Hz), 7.81(1H, d, J=2.0Hz), 7.88(2H, d, J=6.3Hz),
5 8.73(2H, d, J=6.3Hz), 9.35(2H, s), 12.45(1H, s).

MS (FAB) m/z: 497 [(M+H)⁺, Cl³⁵], 499 [(M+H)⁺, Cl³⁷].

[Example A-210] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-
4-[4-(pyridin-4-yl)benzylidene]piperazine

10 In the same manner as in Referential Example 7, the
title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.45-2.52(2H, m), 2.57-2.61(2H, m), 3.12-
3.16(2H, m), 3.20-3.24(2H, m), 6.44(1H, s),
7.37(2H, d, J=8.3Hz), 7.56(1H, dd, J=8.5, 2.0Hz),
7.91(2H, d, J=8.3Hz), 8.05(1H, d, J=8.5Hz), 8.07(1H, s),
15 8.16(2H, d, J=6.6Hz), 8.31(1H, s), 8.82(2H, d, J=6.6Hz).

HRMS (FAB) m/z: 481.0783 (M+H)⁺ (calcd for C₂₅H₂₂ClN₂O₂S₂,
481.0811).

[Example A-211] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
[[5-(2-methylpyridin-4-yl)pyrimidin-2-
20 yl]carbonyl]piperazine

In the same manner as in Example A-182, the title
compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.69(3H, s), 2.93(2H, br s), 3.13(2H, br
s), 3.37(2H, br s), 3.80(2H, br s), 7.75(1H, dd, J=8.8 and
25 2.0Hz), 7.84(1H, d, J=7.8Hz), 8.10(1H, br s), 8.18-8.23(2H, m),

8.26-8.32 (2H, m), 8.53 (1H, br s), 8.82 (1H, d, J=5.9 Hz),
9.38 (2H, s).

MS (FAB) m/z: 508 [(M+H)⁺, Cl³⁵], 510 [(M+H)⁺, Cl³⁷].

[Example A-212] 4-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-methylpyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.60 (3H, s), 3.13-3.17 (2H, m), 3.25-
3.28 (2H, m), 3.55-3.59 (2H, m), 3.94-3.98 (2H, m),
7.37 (1H, dd, J=6.8 and 2.9 Hz), 7.49 (1H, d, J=2.9 Hz),
7.60 (1H, dd, J=8.8 and 2.0 Hz), 7.76 (1H, dd, J=8.8 and 2.0 Hz),
7.90-7.97 (3H, m), 8.31 (1H, d, J=2.0 Hz), 8.37 (1H, d, J=6.8 Hz),
8.97 (2H, s).

MS (FAB) m/z: 524 [(M+H)⁺, Cl³⁵], 526 [(M+H)⁺, Cl³⁷].

[Example A-213] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.93 (2H, br s), 3.12 (2H, br s),
3.36 (2H, br s), 3.81 (2H, br s), 7.50 (1H, dd, J=7.3 and 4.9 Hz),
7.74 (1H, dd, J=8.8 and 2.0 Hz), 7.83 (1H, dd, J=8.8 and 1.5 Hz),
7.96-8.03 (1H, m), 8.16 (1H, d, J=8.3 Hz), 8.19 (1H, d, J=8.8 Hz),
8.25-8.31 (2H, m), 8.52 (1H, br s), 8.75 (1H, d, J=4.9 Hz),
9.46 (2H, s).

MS (FAB) m/z: 494 [(M+H)⁺, Cl³⁵], 496 [(M+H)⁺, Cl³⁷].

[Example A-214] 2-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

5 In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 3.13-3.16(2H,m), 3.24-3.27(2H,m), 3.57-3.60(2H,m), 3.93-3.97(2H,m), 7.38-7.44(2H,m), 7.46-7.50(1H,m), 7.59(1H,dd,J=8.8 and 2.0Hz), 7.77(1H,dd,J=8.8 and 2.0Hz), 7.91-7.96(3H,m), 8.31(1H,br s), 8.35-8.38(1H,m), 9.26(2H,s).

MS (FAB) m/z: 510 [(M+H)⁺, Cl³⁵], 512 [(M+H)⁺, Cl³⁷].

[Example A-215] 1-[[5-(Pyridin-4-yl)pyrimidin-2-yl]carbonyl]-4-[(6-trimethylsilylethynylbenzo[b]thien-2-yl)sulfonyl]piperazine

15 In a 1N aqueous hydrochloric acid in ethanol was dissolved 1-(tert-butoxycarbonyl)-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine (739 mg), followed by stirring at room temperature for 30 minutes. The solvent was distilled off under reduced pressure. To the residue were added N,N-dimethylformamide (15 ml), triethylamine (2 ml) and 6-trimethylsilylethynylbenzo[b]thiophen-2-sulfonyl chloride (740 mg) and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with methylene chloride, washed with water (thrice), dried over anhydrous sodium sulfate and purified

by chromatography on a silica gel column (hexane : ethyl acetate = 1:0 → 1:1 → ethyl acetate : methylene chloride = 3:1 → 0:1 → methylene chloride : methanol = 100:2 → 100:7), whereby the title compound (167 mg) was obtained as a white solid.

¹H-NMR (CDCl₃) δ: 0.28 (9H, s), 3.25 (2H, t, J=4.9 Hz), 3.35 (2H, t, J=4.9 Hz), 3.61 (2H, t, J=4.9 Hz), 4.00 (2H, t, J=4.9 Hz), 7.51 (2H, dd, J=4.4, 1.5 Hz), 7.55 (1H, dd, J=8.3, 1.5 Hz), 7.78 (1H, s), 7.83 (1H, d, J=8.3 Hz), 8.00 (1H, s), 8.80 (2H, dd, J=4.4, 1.5 Hz), 9.03 (2H, s).

MS (FAB) m/z: 567 (M+H)⁺.

[Example A-216] 4-[[5-(Pyridin-4-yl)pyrimidin-2-yl]carbonyl]-1-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]piperazine

In a mixed solvent of tetrahydrofuran (5 ml) and methanol (7 ml) was dissolved 1-[[5-(4-pyridyl)pyrimidin-2-yl]carbonyl]-4-[(6-trimethylsilylethynylbenzo[b]thien-2-yl)sulfonyl]piperazine (167 mg), followed by the addition of potassium hydroxide (34 mg). The resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was made weakly acidic with a saturated aqueous solution of ammonium chloride, and then made weakly alkaline with a saturated aqueous solution of sodium bicarbonate. After concentration under reduced pressure, the concentrate was extracted (4 times) with methylene

chloride. The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : methanol = 1:0 → 24:1). The resulting amorphous was dissolved in methylene chloride, followed by the dropwise addition to hexane to precipitate the resulting mixture as powder. The title compound (112 mg) was obtained as a white solid.

¹H-NMR (CDCl₃) δ: 3.23(1H,s), 3.25(2H,t,J=5.1Hz), 3.35(2H,t,J=5.1Hz), 3.61(2H,t,J=5.1Hz), 4.00(2H,t,J=5.1Hz), 7.51(2H,dd,J=4.4,1.5Hz), 7.58(1H,dd,J=8.3,0.98Hz), 7.79(1H,s), 7.86(1H,d,J=8.3Hz), 8.02(1H,s), 8.80(2H,dd,J=4.4,1.5Hz), 9.02(2H,s).

MS (FAB) m/z: 490 (M+H)⁺.

[Example A-217] 1-[(5-Chloroisoindolin-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example A-4, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 3.22-3.80(8H,m), 4.63-4.65(4H,m), 7.37(1H,d,J=8.3Hz), 7.37(1H,m), 7.43(1H,s), 7.64(2H,d,J=8.3Hz), 8.04(2H,d,J=8.3Hz), 8.20-8.14(2H,br), 8.9(2H,d,J=5.4Hz).

MS (FAB) m/z: 483 [(M+H)⁺, Cl³⁵], 485 [(M+H)⁺, Cl³⁷].

[Example A-218] 4-[4-[4-[(5-Chloroisoindolin-2-

yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.25-3.77 (8H,m), 4.62-4.65 (4H,m), 7.33-
 5 7.39 (2H,m), 7.43 (1H,s), 7.54 (2H,d,J=8.3Hz),
 7.81 (1H,d,J=6.8Hz), 7.86 (2H,d,J=8.3Hz), 8.28 (2H,d,J=6.8Hz).
 MS (FAB) m/z: 499 [(M+H)⁺, Cl³⁵], 501 [(M+H)⁺, Cl³⁷].

[Example A-219] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-ethyl-
 1-[[5-pyridin-4-yl]pyrimidin-2-yl]carbonyl]piperazine

10 In the same manner as in Example A-182, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 0.75 (1.5H,t,J=7.8Hz),
 0.94 (1.5H,t,J=7.8Hz), 1.60-1.89 (2H,m), 2.23-2.57 (2H,m),
 3.14 (0.5H,m), 3.25-3.43 (1H,m), 3.45-3.90 (2.5H,m), 4.44-
 15 4.53 (0.5H,m), 4.65-4.72 (0.5H,m), 7.04 (1H,t,J=2.4Hz),
 7.34 (1H,dt,J=8.8,2.4Hz), 7.50 (1H,dd,J=8.8,2.4Hz),
 7.80 (1H,t,J=2.4Hz), 8.18 (2H,br), 8.90 (2H,br),
 9.39 (2H,t,J=2.4Hz), 12.48 (1H,br).
 MS (FAB) m/z: 511 [(M+H)⁺, Cl³⁵], 513 [(M+H)⁺, Cl³⁷].

20 [Example A-220] 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-ethylpiperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

25 ¹H-NMR (DMSO-d₆) δ: 0.74 (1.5H,t,J=7.3Hz),

0.93 (1.5H, t, J=7.3Hz), 1.03-1.09 (0.5H, m), 1.58-1.68 (0.5H, m),
 1.70-1.90 (1.5H, m), 2.13-2.57 (2H, m), 3.13-3.21 (0.5H, m),
 3.25-3.60 (2H, m), 3.70-3.76 (0.5H, m), 3.78-3.86 (0.5H, m),
 4.45-4.52 (0.5H, m), 4.67 (0.5H, br), 7.04 (1H, m),
 5 7.34 (1H, dt, J=8.8, 2.4Hz), 7.50 (1H, dd, J=8.8, 2.4Hz),
 7.80 (1H, t, J=2.4Hz), 7.90 (2H, dd, J=7.3, 2.4Hz),
 8.38 (2H, t, J=7.3, 3.4Hz), 9.29 (2H, d, J=4.5Hz), 12.46 (1H, br).
 MS (FAB) m/z: 517 [(M+H)⁺, Cl³⁵], 519 [(M+H)⁺, Cl³⁷].

[Example A-221] 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-
 10 2-ethyl-1-[(5-(pyridin-4-yl)pyrimidin-2-
 yl)carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 0.77 (1.5H, t, J=7.8Hz),
 15 0.95 (1.5H, t, J=7.8Hz), 1.62-1.70 (0.5H, m), 1.73-1.82 (0.5H, m),
 1.83-1.93 (1H, m), 2.44-2.71 (2H, m), 3.14-3.24 (0.5H, m), 3.35-
 3.62 (2H, m), 3.67-3.76 (1H, m), 3.79-3.85 (0.5H, m), 4.47-
 4.53 (0.5H, m), 4.67-4.74 (0.5, m), 7.57-7.62 (1H, m), 8.03-
 8.14 (4H, m), 8.33-8.37 (1H, m), 8.83 (1H, d, J=4.6Hz),
 20 9.36 (2H, d, J=3.7Hz).

MS (FAB) m/z: 528 [(M+H)⁺, Cl³⁵], 530 [(M+H)⁺, Cl³⁷].

[Example A-222] 4-[2-[[4-[(6-Chlorobenzo[b]thien-2-
 yl)sulfonyl]-2-ethylpiperazin-1-yl]carbonyl]pyrimidin-5-
 yl]pyridine N-oxide

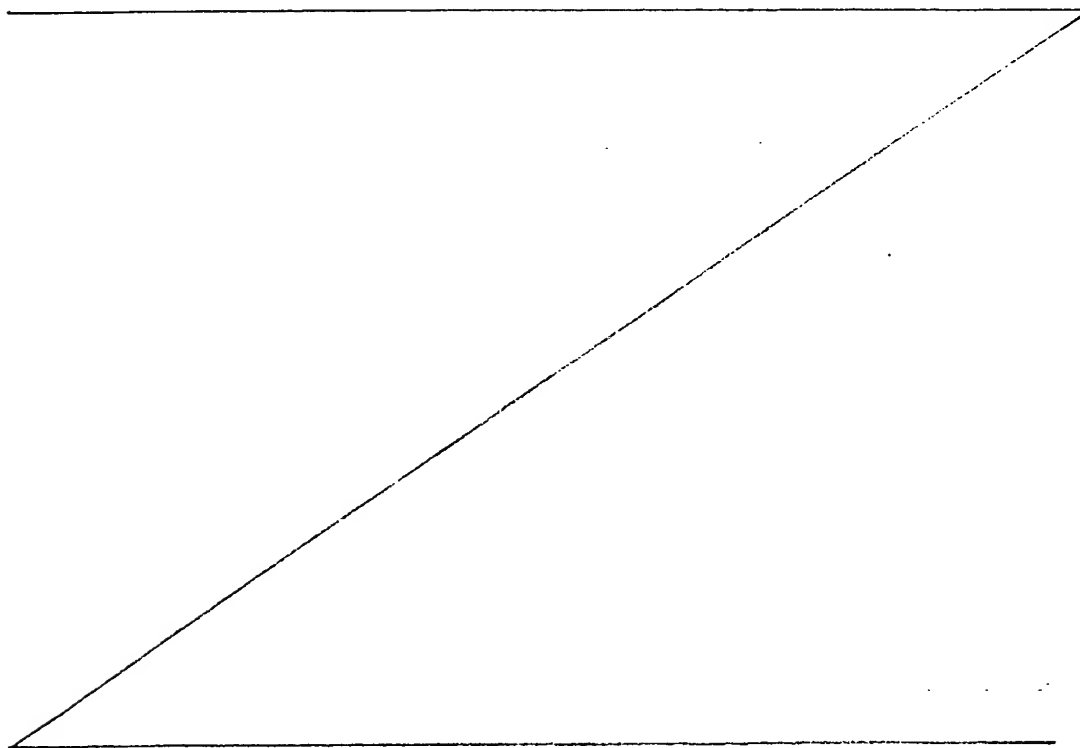
25 In the same manner as in Example A-6, the title compound was obtained.

^1H -NMR (DMSO- d_6) δ : 0.76 (1.5H, t, $J=7.3\text{Hz}$),
0.94 (1.5H, t, $J=7.3\text{Hz}$), 1.15-1.28 (0.5H, m), 1.60-1.69 (0.5H, m),
1.70-1.92 (1.5H, m), 2.50-2.60 (1H, m), 2.62-2.71 (1H, m), 3.12-
3.24 (0.5H, m), 3.35-3.45 (1H, m), 3.50-3.61 (1H, m), 3.64-
5 3.87 (1H, m), 4.47-4.54 (0.5H, m), 4.67-4.74 (0.5H, m), 7.58-
7.63 (1H, m), 7.94-8.00 (2H, m), 8.06-8.13 (2H, m), 8.34-
8.40 (3H, m), 9.30 (2H, d, $J=2.0\text{Hz}$).

MS (FAB) m/z : 544 $[(M+H)^+, \text{Cl}^{35}]$, 546 $[(M+H)^+, \text{Cl}^{37}]$.

[Example A-223] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-ethyl-
10 1-[(5-(pyridin-2-yl)pyrimidin-2-yl)carbonyl]piperazine

In the same manner as in Example A-182, the title
compound was obtained.



¹H-NMR (DMSO-d₆) δ: 0.74 (1.5H, t, J=7.3Hz),
 0.94 (1.5H, t, J=7.3Hz), 1.02-1.13 (0.5H, m), 1.57-1.68 (0.5H, m),
 1.70-1.89 (2H, m), 2.25-2.49 (1H, m), 3.10-3.23 (0.5H, m), 3.27-
 3.59 (2.5H, m), 3.68-3.87 (1H, m), 4.45-4.52 (0.5H, m), 4.63-
 5 4.71 (0.5H, m), 7.03-7.05 (1H, m), 7.32-7.36 (1H, m),
 7.50 (2H, d, J=8.3, 2.4Hz), 7.79 (1H, br), 7.98-8.02 (1H, m),
 8.16 (1H, d, J=7.8Hz), 8.75-8.77 (1H, m), 9.48 (2H, br),
 12.46 (1H, br).

MS (FAB) m/z: 511 [(M+H)⁺, Cl³⁵], 513 [(M+H)⁺, Cl³⁷].

10 [Example A-224] 2-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-
 ethylpiperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-
 oxide

To a methylene chloride solution (50 ml) of 4-[(5-
 chloroindol-2-yl)sulfonyl]-2-(ethyl)-1-[(5-(pyridin-2-
 15 yl)pyrimidin-2-yl]carbonyl]piperazine (234 mg) was added
 metachloroperbenzoic acid (1.58 g) at room temperature.
 The resulting mixture was stirred for 5 hours. An aqueous
 solution (20 ml) of sodium sulfite was added, followed by
 stirring for 1 hour. To the reaction mixture were added a
 20 saturated aqueous solution of sodium bicarbonate and
 methylene chloride. The water layer was extracted thrice
 with methylene chloride. The organic layers were combined,
 dried over anhydrous sodium sulfate and distilled under
 reduced pressure to remove the solvent. The residue was
 25 subjected to chromatography on a silica gel column
 (methanol : methylene chloride = 1:50). The oil thus

obtained was solidified from ethanol - diethyl ether, whereby the title compound (44.1 mg) was obtained as a pale yellow solid.

MS (FAB) m/z: 527 [(M+H)⁺, Cl³⁵], 529 [(M+H)⁺, Cl³⁷].

5 ¹H-NMR (DMSO-d₆) δ: 0.75 (1.5H, t, J=7.3Hz),
 0.93 (1.5H, t, J=7.3Hz), 1.05-1.13 (0.5H, m), 1.58-1.92 (2.5H, m),
 2.29-2.78 (1H, m), 3.13-3.89 (4H, m), 4.40-4.52 (0.5H, m), 4.62-
 4.71 (0.5H, m), 7.04 (1H, d, J=3.4Hz), 7.32-7.37 (1H, m), 7.47-
 7.55 (3H, m), 7.78-7.82 (1H, m), 7.86-7.90 (1H, m),
 10 8.42 (1H, d, J=5.9Hz), 9.33 (2H, br), 12.44 (1H, br).

[Example A-225] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[5-(pyridin-3-yl)thiazol-2-yl]piperazine

To a solution of 3-(5-thiazolyl)pyridine (400 mg) in diethyl ether (15 mg), n-butyl lithium (a 1.52 N hexane
 15 solution, 1.45 ml) was added dropwise at -78°C. After stirring for 30 minutes, a carbon dioxide gas was blown into the reaction mixture. After 10 minutes, a cooling bath was removed and the temperature of the reaction mixture was allowed to rise back slowly to room
 20 temperature. The reaction mixture was concentrated, whereby the residue of lithium 5-(3-pyridyl)thiazole-2-carboxylate was obtained as a white solid. To a solution of the resulting residue in N,N-dimethylformamide (10 ml) were added 1-[(5-chloroindol-2-yl)sulfonyl]piperazine
 25 hydrochloride (600 mg), 1-hydroxybenzotriazole monohydrate (255 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

hydrochloride (360 mg) at room temperature. After stirring for 3 days, ethyl acetate (50 ml) and water (100 ml) were added to the reaction mixture. The white precipitate thus obtained was collected by filtration and washed with water and ethyl acetate, whereby the title compound (727 mg) was obtained as a pale brown solid. A portion of the compound was added with an aqueous solution of hydrochloric acid, followed by concentration and drying. The product thus obtained showed the following data.

¹H-NMR (DMSO-d₆) δ: 3.32(4H,br s), 3.94(2H,br s), 4.59(2H,br s), 7.20(1H,s), 7.47(1H,d,J=8.8Hz), 7.65(1H,d,J=8.8Hz), 7.66-7.76(1H,m), 7.93(1H,s), 8.36(1H,d,J=8.3Hz), 8.63(1H,br s), 8.78(1H,s), 9.16(1H,s), 12.61(1H,s).

MS (FAB) m/z: 488 (M+H)⁺.

[Example A-226] 3-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.31(4H,br s), 3.93(2H,br s), 4.57(2H,br s), 7.19(1H,s), 7.46(1H,d,J=8.8Hz), 7.50-7.70(2H,m), 7.80(1H,d,J=8.3Hz), 7.92(1H,s), 8.05(1H,s), 8.39(1H,d,J=6.4Hz), 8.67(1H,br s), 8.93(1H,s), 12.61(1H,br s).

MS (FAB) m/z : 504 (M+H)⁺, 488 (M+H-O)⁺.

[Example A-227] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-4-[5-(2-methylpyridin-4-yl)thiazol-2-yl]piperazine

5 A saturated solution of hydrochloride in methanol (12 ml) was added to 1-(t-butoxycarbonyl)-4-[5-(2-methylpyridin-4-yl)thiazol-2-yl]piperazine (400 mg) at room temperature. After stirring for 10 minutes, the reaction mixture was concentrated under reduced pressure, whereby 1-

10 [5-(2-methylpyridin-4-yl)thiazol-2-yl]piperazine hydrochloride was obtained as a white solid. In a solution of the resulting hydrochloride in methylene chloride (12 ml) was dissolved 5-chloro-1-phenylsulfonylindol-2-sulfonyl chloride (522 mg), followed by the addition of

15 diisopropylethylamine (538 μ l) at room temperature. After stirring for 3 hours, a saturated aqueous solution (50 ml) of sodium bicarbonate was added to the reaction mixture to separate it into layers. The water layer was extracted with methylene chloride (2 x 15 ml). The organic layers

20 were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 7:1), whereby the title compound (240 mg) was obtained as a foam.

25 ¹H-NMR (CDCl₃) δ : 2.63(3H,s), 3.55(2H,s), 3.60(2H,s), 3.92(2H,s), 4.60(2H,s), 7.31(1H,d,J=5.4Hz), 7.35(1H,s),

7.40-7.52 (4H,m), 7.52-7.65 (2H,m), 8.03 (2H,d,J=7.3Hz),
8.14 (1H,s), 8.23 (1H,d,J=9.3Hz), 8.56 (1H,d,J=5.4Hz).

[Example A-228] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[5-(2-methylpyridin-4-yl)thiazol-2-yl]piperazine

5 In the same manner as in Example A-99, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.88 (3H,s), 3.33 (4H,br s), 3.95 (2H,br s), 4.57 (2H,br s), 7.20 (1H,d,J=2.0Hz),
7.47 (1H,dd,J=8.8,2.0Hz), 7.66 (1H,d,J=8.8Hz),
10 7.93 (1H,d,J=2.0Hz), 8.32 (1H,d,J=6.4Hz), 8.40 (1H,br s),
8.94 (1H,d,J=6.4Hz), 9.02 (1H,d,J=2.0Hz), 12.66 (1H,s).
MS (FAB) m/z: 502 [(M+H)⁺, Cl³⁵], 504 [(M+H)⁺, Cl³⁷].

[Example A-229] 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]-2-methylpyridine N-oxide
15

In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.28 (4H,br s), 3.47 (3H,s), 3.91 (2H,br),
4.56 (2H,br s), 7.17 (1H,s), 7.44 (1H,dd,J=8.8,2.0Hz),
20 7.62 (1H,d,J=8.8Hz), 7.81 (1H,dd,J=6.8,2.7Hz),
7.90 (1H,d,J=2.0Hz), 8.04 (1H,d,J=2.7Hz), 8.43 (1H,d,J=6.8Hz),
8.59 (1H,s), 12.57 (1H,br s).
MS (FAB) m/z: 518 (M+H)⁺, 502 (M+H-O)⁺.

[Example A-230] 1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[5-(pyridin-4-yl)thiazol-2-yl]piperazine
25

A saturated solution of hydrochloride in methanol (12 ml) was added to 1-(tert-butoxycarbonyl)-4-[5-(pyridin-4-yl)thiazol-2-yl]piperazine (400 mg) at room temperature. After stirring for 1 hour, the reaction mixture was concentrated under reduced pressure, whereby the residue, that is, 1-[5-(pyridin-4-yl)thiazol-2-yl]piperazine hydrochloride was obtained as a white solid. In a solution of the resulting residue in methylene chloride (15 ml) was dissolved [1-phenylsulfonyl-5-(trimethylsilylethynyl)indol-2-yl]sulfonyl chloride (630 mg), followed by the addition of diisopropylethylamine (746 μ l) at 0 °C. After stirring for 4 hours, methylene chloride (10 ml) and a saturated aqueous solution (30 ml) of sodium bicarbonate were added to the reaction mixture to separate it into layers. The water layer was extracted with methylene chloride (2 x 10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 6:1), whereby 1-[5-(2-methylpyridin-4-yl)thiazol-2-yl]-4-[[1-phenylsulfonyl-5-(trimethylsilylethynyl)indol-2-yl]sulfonyl]piperazine (214 mg) was obtained as a foam. To a solution of the resulting residue in tetrahydrofuran (10 ml) were added methanol (10 ml), morpholine (54.0 μ l) and potassium hydroxide (52.0 mg), followed by stirring at room temperature for 3 hours. A saturated aqueous solution

(30 ml) of sodium bicarbonate, methylene chloride (30 ml) and water (10 ml) were added to the reaction mixture to separate it into layers. The water layer was extracted with methylene chloride (10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by preparative thin-layer chromatography (methylene chloride : acetone = 6:1) using silica gel, whereby the title compound (84.8 mg) was obtained as a white solid. The solid was dissolved in tetrahydrofuran, followed by the addition of water. The resulting mixture was concentrated, whereby a white solid was obtained. The solid showed the following data:

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.15(4H, br s), 3.77(2H, br s), 4.01(1H, s), 4.41(2H, br s), 7.05(1H, s), 7.34(1H, d, $J=8.5\text{Hz}$), 7.44(1H, d, $J=8.5\text{Hz}$), 7.72(2H, d, $J=4.9\text{Hz}$), 7.85(1H, s), 8.58(1H, s), 8.63(2H, d, $J=4.9\text{Hz}$), 12.42(1H, br s).

MS (FAB) m/z : 478 ($\text{M}+\text{H}$) $^+$.

[Example A-231] 4-[2-[[4-[(5-Ethynylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.16(4H, br s), 3.77(2H, br s), 4.02(1H, s), 4.41(2H, br s), 7.06(1H, s), 7.36(1H, d, $J=8.5\text{Hz}$), 7.46(1H, d, $J=8.5\text{Hz}$), 7.78(2H, d, $J=6.9\text{Hz}$), 7.86(1H, s),

8.26(2H,d,J=6.9Hz), 8.48(1H,s), 12.43(1H,br s).

MS (FAB) m/z: 494 (M+H)⁺, 478 (M+H-O)⁺.

[Example A-232] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
[[5-(pyridin-4-yl)thiazol-2-yl]carbonyl]piperazine
5 hydrochloride

In the same manner as in Example A-7, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.14(4H,br s), 3.79(2H,br s),

4.41(2H,br s), 7.71(1H,dd,J=8.8,2.0Hz),

10 7.83(1H,dd,J=8.8,2.0Hz), 8.11(2H,d,J=5.9Hz),

8.15(1H,d,J=8.8Hz), 8.22(1H,d,J=2.0Hz), 8.25(1H,d,J=8.8Hz),

8.51(1H,s), 8.77(1H,s), 8.79-8.85(2H,m).

MS (FAB) m/z: 499 [(M+H)⁺, Cl³⁵], 501 [(M+H)⁺, Cl³⁷].

[Example A-233] 4-[2-[[4-[(6-Chloronaphthalen-2-
15 yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine
N-oxide

In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.13(4H,br s), 3.77(2H,br s),

20 4.43(2H,br s), 7.69(1H,d,J=8.8Hz), 7.76(2H,d,J=6.4Hz),

7.82(1H,d,J=8.8Hz), 8.15(1H,d,J=8.8Hz), 8.20-8.28(5H,m),

8.46(1H,s), 8.50(1H,s).

MS (FAB) m/z: 515 [(M+H)⁺, Cl³⁵], 517 [(M+H)⁺, Cl³⁷].

[Example A-234] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
25 [[5-(pyridin-2-yl)thiazol-2-yl]carbonyl]piperazine

hydrochloride

In the same manner as in Example A-4, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.13(4H, br s), 3.77(2H, br s),
 5 4.42(2H, br s), 7.37(1H, m), 7.69(1H, dd, J=8.8, 2.0Hz),
 7.81(1H, d, J=8.8Hz), 7.89(1H, m), 8.03(1H, d, J=7.8Hz),
 8.15(1H, d, J=8.8Hz), 8.21(1H, d, J=2.0Hz), 8.25(1H, d, J=8.8Hz),
 8.50(1H, s), 8.56(1H, s), 8.57(1H, d, J=4.4Hz).

MS (FAB) m/z: 499 [(M+H)⁺, Cl³⁵], 501 [(M+H)⁺, Cl³⁷].

10 [Example A-235] 2-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

15 ¹H-NMR (DMSO-d₆) δ: 3.14(4H, br s), 3.78(2H, br s),
 4.41(2H, br s), 7.47(1H, t, J=7.8Hz), 7.54(1H, t, J=7.8Hz),
 7.68(1H, dd, J=8.8, 2.0Hz), 7.84(1H, d, J=8.8Hz),
 8.15(1H, d, J=8.8Hz), 8.20(1H, s), 8.25(1H, d, J=8.8Hz), 8.42-
 8.51(3H, m), 8.95(1H, s).

20 MS (FAB) m/z: 515 [(M+H)⁺, Cl³⁵], 517 [(M+H)⁺, Cl³⁷].

[Example A-236] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)thiazol-2-yl]carbonyl]piperazine hydrochloride

In the same manner as in Example A-4, the title
 25 compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.18(4H,br s), 3.80(2H,br s),
4.41(2H,br s), 7.04(1H,s), 7.30(1H,dd,J=8.8,1.5Hz),
7.49(1H,d,J=8.8Hz), 7.76(1H,s), 8.15(2H,d,J=5.9Hz),
8.79(1H,s), 8.84(2H,d,J=5.9Hz), 12.44(1H,s).

5 MS (FAB) m/z: 488 [(M+H)⁺, Cl³⁵], 490 [(M+H)⁺, Cl³⁷].

[Example A-237] 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine
N-oxide

10 In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.16(4H,br s), 3.78(2H,br s),
4.43(2H,br s), 7.03(1H,s), 7.30(1H,dd,J=8.8,2.0Hz),
7.47(1H,d,J=8.8Hz), 7.75(1H,d,J=2.0Hz), 7.77(2H,d,J=7.3Hz),
8.25(2H,d,J=7.3Hz), 8.30(1H,s), 8.47(1H,s), 12.41(1H,s).

15 MS (FAB) m/z: 504 [(M+H)⁺, Cl³⁵], 506 [(M+H)⁺, Cl³⁷].

[Example A-238] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-
4-[[5-(pyridin-4-yl)thiazol-2-yl]carbonyl]piperazine
hydrochloride

20 In the same manner as in Example A-4, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.24(4H,br s), 3.84(2H,br s),
4.46(2H,br s), 7.50-7.65(3H,m), 8.03-8.10(2H,m),
8.30(1H,s), 8.76(1H,s), 8.80(2H,m).

MS (FAB) m/z: 505 [(M+H)⁺, Cl³⁵], 507 [(M+H)⁺, Cl³⁷].

25 [Example A-239] 4-[2-[[4-[(6-Chlorobenzo[b]thien-2-

yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine
N-oxide

In the same manner as in Example A-6, the title
compound was obtained.

5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 3.22 (4H, br s), 3.82 (2H, br s),
4.47 (2H, br s), 7.54 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.78 (2H, d, $J=7.3\text{Hz}$),
8.05 (1H, d, $J=8.8\text{Hz}$), 8.09 (1H, s), 8.25 (2H, d, $J=7.3\text{Hz}$),
8.29 (1H, s), 8.48 (1H, s).

MS (FAB) m/z : 521 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 523 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

10 [Example A-240] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[3-
(pyridin-4-yl)-1,2,4-triazin-6-yl]carbonyl]piperazine
hydrochloride

Ethyl 3-(pyridin-4-yl)-1,2,4-triazin-6-carboxylate
(200 mg) was dissolved in a mixed solvent of
15 tetrahydrofuran (5 ml) and methanol (5 ml) at room
temperature. A 1N aqueous solution (1.00 ml) of sodium
hydroxide was added to the reaction mixture in one portion.
After stirring for 5 minutes, the reaction mixture was
distilled under reduced pressure to remove tetrahydrofuran
and methanol, followed by neutralization with 1N
20 hydrochloric acid. The reaction mixture was concentrated
to dryness, whereby 3-(pyridin-4-yl)-1,2,4-triazine-6-
carboxylic acid was obtained as a crudely purified product.

In N,N-dimethylformamide (10 ml) were suspended 3-
25 (pyridin-4-yl)-1,2,4-triazine-6-carboxylic acid and 1-[(5-
chloroindol-2-yl)sulfonyl]piperazine hydrochloride (292 mg)

at room temperature. To the reaction mixture were successively added 1-hydroxybenzotriazole (117 mg), N-methylmorpholine (191 μ l) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (250 mg), followed by stirring overnight. After completion of the reaction, the solvent was distilled off under reduced pressure. Water and ethyl acetate were added to the residue to separate into layers. The organic layer was dried over magnesium sulfate and the filtrate was concentrated. Ethanol was added to the residue. Yellow crystals thus precipitated were collected by filtration and dried, whereby the free form (282 mg) of the title compound was obtained. The free form was suspended in ethanol and the resulting suspension was made acidic by the addition of 1N hydrochloric acid (in ethanol) and a small amount of water. After concentration of the resulting solution, ethanol and ethyl acetate were added and the resulting mixture was concentrated again. Crystals thus precipitated were collected by filtration and dried, whereby the title compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.05-3.09(2H,m), 3.18-3.21(2H,m), 3.69-3.72(2H,m), 3.84-3.88(2H,m), 7.05(1H,d,J=1.5Hz), 7.33(1H,dd,J=8.8,2.0Hz), 7.50(1H,d,J=8.8Hz), 7.79(1H,d,J=2.0Hz), 8.45-8.52(2H,m), 8.92-8.98(2H,m), 9.17(1H,d,J=1.0Hz), 12.47(1H,s).

MS (FAB) m/z : 484 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 486 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Example A-241] 4-[6-[[4-[(5-Chloroindol-2-

yl)sulfonyl]piperazin-1-yl]carbonyl]-1,2,4-triazin-3-yl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 3.06(2H,br), 3.18(2H,br), 3.70(2H,br), 3.85(2H,br), 7.05(1H,s), 7.32(1H,dd, $J=8.8, 2.0\text{Hz}$), 7.49(1H,d, $J=8.8\text{Hz}$), 7.79(1H,d, $J=2.0\text{Hz}$), 8.34(2H,d, $J=7.3\text{Hz}$), 8.40(2H,d, $J=7.3\text{Hz}$), 9.06(1H,s), 12.45(1H,s).
MS (FAB) m/z : 500 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 502 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

10 [Example A-242] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[2,5-dihydro-5-oxo-6-(pyridin-4-yl)-1,2,4-triazin-3-yl]carbonyl]piperazine hydrochloride

In the same manner as in Example A-4, the title compound was obtained.

15 $^1\text{H-NMR}$ (DMSO-d_6) δ : 3.00-3.09(2H,m), 3.10-3.17(2H,m), 3.75-3.81(4H,m), 7.74(1H,dd, $J=8.8$ and 2.0Hz), 7.86(1H,d, $J=8.8\text{Hz}$), 8.20(1H,d, $J=8.8\text{Hz}$), 8.25-8.35(4H,m), 8.55(1H,br s), 8.86(2H,d, $J=5.4\text{Hz}$).
MS (FAB) m/z : 511 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 513 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

20 [Example A-243] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(2,6-dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine hydrochloride

In the same manner as in Example A-182, the title compound was obtained.

25 $^1\text{H-NMR}$ (DMSO-d_6) δ : 2.71(6H,s), 2.94(2H,br s), 3.13(2H,br

s), 3.37 (2H, br s), 3.80 (2H, br s), 7.74 (1H, dd, J=8.8, 2.0 Hz), 7.83 (1H, d, J=8.8 Hz), 8.13 (2H, br s), 8.13 (1H, d, J=8.8 Hz), 8.27-8.30 (2H, m), 8.52 (1H, s), 9.38 (2H, s).

MS (FAB) m/z: 522 [(M+H)⁺, Cl³⁵], 524 [(M+H)⁺, Cl³⁷].

5 [Example A-244] 4-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,6-dimethylpyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

10 ¹H-NMR (CDCl₃) δ: 2.61 (6H, s), 3.15 (2H, d, J=4.8 Hz), 3.26 (2H, d, J=4.8 Hz), 3.57 (2H, d, J=4.8 Hz), 3.96 (2H, d, J=4.9 Hz), 7.37 (2H, s), 7.60 (1H, dd, J=8.8, 2.0 Hz), 7.76 (1H, dd, J=8.8, 1.5 Hz), 7.91-7.97 (3H, m), 8.31 (1H, s), 8.96 (2H, s).

15 MS (FAB) m/z: 538 [(M+H)⁺, Cl³⁵], 540 [(M+H)⁺, Cl³⁷].

[Example A-245] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)phenylsulfonyl]piperazine

A saturated solution of hydrochloride in methanol (10 ml) was added to 1-(tert-butoxycarbonyl)-4-[4-(pyridin-4-yl)phenylsulfonyl]piperazine (180 mg). After stirring for 30 minutes, the solvent was distilled off under reduced pressure. To the residue were added methylene chloride (10 ml), 5-chloro-1-phenylsulfonylindol-2-sulfonyl chloride (260 mg) and diisopropylethylamine (235 µg) at room temperature. After stirring for 4 hours, methylene chloride (10 ml) and a saturated aqueous solution (30 ml)

of sodium bicarbonate were added the reaction mixture to separate it into layers. The water layer was extracted with methylene chloride. The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 5:1 → 3:1), whereby the title compound (131 mg) was obtained as a pale yellow foam.

¹H-NMR (CDCl₃) δ: 3.18(4H,s), 3.57(4H,s), 7.37-7.46(4H,m), 7.50-7.59(4H,m), 7.80(2H,d,J=8.3Hz), 7.85(2H,d,J=8.3Hz), 7.86(2H,d,J=8.3Hz), 8.12(1H,d,J=8.8Hz), 8.76(2H,br d,J=4.4Hz).

[Example A-246] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)phenylsulfonyl]piperazine hydrochloride

In the same manner as in Example A-103, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.05(4H,br t,J=4.0Hz), 3.18(4H,br t,J=4.0Hz), 6.97(1H,d,J=1.5Hz), 7.16(1H,dd,J=8.8,1.9Hz), 7.40(1H,d,J=8.8Hz), 7.68(1H,d,J=1.9Hz), 7.83(2H,d,J=8.5Hz), 8.09(2H,d,J=8.5Hz), 8.19(2H,d,J=6.6Hz), 8.97(2H,d,J=6.6Hz), 12.40(1H,br s).

MS (FAB) m/z: 517 (M+H)⁺.

[Example A-247] 4-[4-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]sulfonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, the title

compound was obtained.

^1H -NMR (DMSO- d_6) δ : 3.00 (4H, br t, $J=4.6\text{Hz}$), 3.17 (4H, br t, $J=4.0\text{Hz}$), 6.96 (1H, s), 7.18 (1H, dd, $J=9.1, 1.7\text{Hz}$), 7.39 (1H, d, $J=9.1\text{Hz}$), 7.69 (1H, d, $J=1.7\text{Hz}$), 7.73 (2H, d, $J=8.3\text{Hz}$), 7.82 (2H, d, $J=6.8\text{Hz}$), 7.93 (2H, d, $J=8.3\text{Hz}$), 8.34 (2H, d, $J=6.8\text{Hz}$), 12.35 (1H, br s).

MS (FAB) m/z : 533 ($M+H$) $^+$.

[Example A-248] 1-[(5-Chloroindol-2-yl)carbonyl]-4-[4-(pyridin-4-yl)phenylsulfonyl]piperazine hydrochloride

A saturated solution of hydrochloride in methanol (10 ml) was added to 1-(tert-butoxycarbonyl)-4-[4-(pyridin-4-yl)phenylsulfonyl]piperazine (180 mg). After stirring for 30 minutes, the solvent was distilled off under reduced pressure. To a solution of the residue in N,N -dimethylformamide (10 ml) were added (5-chloroindol-2-yl)carboxylic acid (90.0 mg), 1-hydroxybenzotriazole (75.5 mg) and 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (107 mg) and diisopropylethylamine (233 μg) at room temperature. After stirring for 3 days, methylene chloride (100 ml) and water (500 ml) were added to the reaction mixture to separate it into layers. The water layer was extracted with methylene chloride (50 ml). The organic layers were combined, washed with water (500 ml) and a saturated aqueous solution (100 ml) of sodium bicarbonate, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The

residue was purified by chromatography on a silica gel column (silica gel: 20 g, methylene chloride : acetone = 3:1 → 1:1), whereby the title compound (97.5 mg) was obtained as a white solid. The resulting compound was dissolved in hydrochloric acid - methanol - methylene chloride - tetrahydrofuran, followed by concentration, whereby the title compound was obtained.

Hydrochloride:

¹H-NMR (DMSO-d₆) δ: 3.10(4H, br s), 3.84(4H, br s), 6.76(1H, d, J=1.5Hz), 7.17(1H, dd, J=8.8, 2.0Hz), 7.39(1H, d, J=8.8Hz), 7.62(1H, d, J=2.0Hz), 7.96(2H, d, J=8.3Hz), 8.22(2H, d, J=8.3Hz), 8.30(2H, d, J=6.4Hz), 8.97(2H, d, J=6.4Hz), 11.76(1H, br s).

MS (FAB) m/z: 481 (M+H)⁺.

[Example A-249] 4-[4-[[4-[(5-Chloroindol-2-yl)carbonyl]piperazin-1-yl]sulfonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.07(4H, br s), 3.83(4H, br s), 6.75(1H, s), 7.18(1H, br d, J=8.8Hz), 7.39(1H, d, J=8.8Hz), 7.62(1H, br s), 7.85(2H, d, J=8.3Hz), 7.88(2H, d, J=6.6Hz), 8.07(2H, d, J=8.3Hz), 8.33(2H, d, J=6.6Hz), 11.74(1H, br s).

MS (FAB) m/z: 497 (M+H)⁺.

[Example A-250] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(5-(pyridin-4-yl)pyrimidin-2-yl)carbonyl]-2-(2-

methlpropyl)piperazine

In the same manner as in Example A-182, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 0.84-1.62 (2H,m), 1.75 (3H,s),
 1.77 (3H,s), 2.26-2.41 (1H,m), 2.55-2.70 (1H,m), 3.18-
 3.50 (2H,m), 3.55-3.68 (1H,m), 3.70-4.45 (2H,m), 5.36-
 5.58 (1H,m), 7.04 (1H,s), 7.34 (1H,d,J=8.8Hz),
 7.51 (1H,d,J=8.8Hz), 7.80 (1H,s), 8.16 (2H,br), 8.90 (2H,br),
 9.37 (2H,s), 12.48 (1H,br).

MS (FAB) m/z: 539 [(M+H)⁺, Cl³⁵], 541 [(M+H)⁺, Cl³⁷].

[Example A-251] 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-
 1-[(5-(pyridin-4-yl)pyrimidin-2-yl)carbonyl]-2-(2-
 methylpropyl)piperazine

In the same manner as in Example A-182, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 0.64-1.68 (3H,m), 1.75 (3H,s),
 1.77 (3H,s), 2.25-2.58 (1H,m), 2.60-2.83 (1H,m), 2.87-
 4.23 (4H,m), 4.40-4.53 (1H,m), 7.06 (1H,s),
 7.34 (1H,d,J=8.8Hz), 7.49 (1H,d,J=8.8Hz), 7.81 (1H,s),
 8.15 (2H,br), 8.88 (2H,br), 9.37 (2H,br), 12.48 (1H,s).

MS (FAB) m/z: 556 [(M+H)⁺, Cl³⁵], 558 [(M+H)⁺, Cl³⁷].

[Example A-252] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-2,2-
 dimethyl-4-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example A-4, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.14 (3H, br s), 1.28 (3H, br s), 3.20-3.90 (6H, br), 7.53-7.70 (2H, br), 7.71 (1H, dd, J=8.8, 2.0 Hz), 7.90 (1H, br), 7.96-8.08 (2H, m), 8.14 (1H, d, J=8.8 Hz), 8.20-8.33 (4H, m), 8.57 (1H, s), 8.92 (2H, br).

5 MS (FAB) m/z: 520 [(M+H)⁺, Cl³⁵], 522 [(M+H)⁺, Cl³⁷].

[Example A-253] 4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-3,3-dimethylpiperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

10 In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.26 (3H, br), 1.39 (3H, br), 3.26 (1H, br), 3.50-3.95 (5H, br), 7.45-7.55 (4H, br), 7.58 (1H, dd, J=8.8, 2.0 Hz), 7.62 (2H, d, J=7.8 Hz), 7.79 (1H, d, J=7.8 Hz), 7.89 (2H, d, J=7.8 Hz), 7.92 (1H, s), 8.27 (2H, br), 8.37 (1H, s).

15 MS (FAB) m/z: 536 [(M+H)⁺, Cl³⁵], 538 [(M+H)⁺, Cl³⁷].

[Example A-254] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2,2-dimethyl-1-[4-(pyridin-4-yl)benzoyl]piperazine

20 In the same manner as in Example A-26, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.50 (6H, s), 3.10 (2H, s), 3.20-3.30 (2H, br t), 3.50 (2H, br), 7.58 (2H, d, J=7.8 Hz), 7.73 (1H, dd, J=8.8, 2.0 Hz), 7.87 (1H, dd, J=8.8, 2.0 Hz), 7.98 (2H, d, J=7.8 Hz), 8.19 (1H, d, J=8.8 Hz), 8.20-8.30 (3H, m), 8.30 (1H, d, J=7.8 Hz), 8.53 (1H, s), 8.90 (2H, d, J=5.9 Hz).

25

MS (FAB) m/z : 520 $[(M+H)^+, Cl^{35}]$, 522 $[(M+H)^+, Cl^{37}]$.

[Example A-255] 4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2,2-dimethylpiperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

5 In the same manner as in Example A-6, the title compound was obtained.

1H -NMR ($CDCl_3$) δ : 1.60 (5H, br), 3.04 (2H, s),
3.20 (2H, t, $J=4.9$ Hz), 3.48 (2H, t, $J=4.9$ Hz), 7.40-7.50 (4H, m),
7.56 (2H, d, $J=8.8$ Hz), 7.61 (1H, dd, $J=8.8, 2.0$ Hz),
10 7.79 (1H, dd, $J=8.8, 2.0$ Hz), 7.88-7.96 (1H, m),
7.95 (2H, d, $J=7.8$ Hz), 8.25 (2H, d, $J=7.8$ Hz), 8.34 (1H, s).

MS (FAB) m/z : 536 $[(M+H)^+, Cl^{35}]$, 538 $[(M+H)^+, Cl^{37}]$.

[Example A-256] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(methoxycarbonylmethyl)-1-[[4-(pyridin-4-yl)-3-cyclohexen-
15 1-yl]carbonyl]piperazine

In a mixture of methylene chloride (30 mL) and N,N-dimethylformamide (30 mL) was dissolved 4-(pyridin-4-yl)-3-hexenic acid hydrochloride (480 mg). Under ice cooling, 1-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-2-(methoxycarbonylmethyl)piperazine (1.024 g), 1-hydroxybenzotriazole (405 mg), N-methylmorpholine (607 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (575 mg) were added to the resulting
20 solution. After 10 minutes, the mixture was allowed to
25 rise back to room temperature, followed by stirring. After 48 hours, the reaction was terminated and the solvent was

distilled off under reduced pressure. Ethyl acetate was added to the residue. The resulting mixture was washed with a saturated aqueous solution of sodium bicarbonate and saturated saline, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to chromatography on a silica gel column (methylene chloride : methanol = 20:1), whereby the title compound (680 mg, colorless oil) was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.14 (1H, t, $J=7.1\text{Hz}$), 1.22 (1H, t, $J=7.1\text{Hz}$), 1.64-3.87 (14H, m), 3.69 (3H, s), 6.33-6.42 (1H, m), 6.97 (1H, m), 7.21-7.40 (4H, m), 7.67 (1H, d, $J=2\text{Hz}$), 8.54 (2H, m).

MS (FAB) m/z : 557 ($\text{M}+\text{H}$) $^+$.

[Example A-257] Sodium [4-[(5-chloroindol-2-yl)sulfonyl]-1-[[4-(pyridin-4-yl)-3-cyclohexen-1-yl]carbonyl]piperazin-2-yl]acetate

In a 100-mL egg-plant type flask was charged 4-[(5-chloroindol-2-yl)sulfonyl]-2-(methoxycarbonylmethyl)-1-[[4-(pyridin-4-yl)-3-hexen-1-yl]carbonyl]piperazine (680 mg), followed by dissolution in methanol (20 mL). A 1N sodium hydroxide solution (5 mL) was added to the resulting solution and the resulting mixture was stirred at 70°C. After 23 hours, the reaction was terminated. After concentration, the crystals were collected by filtration, whereby the title compound (320 mg, colorless solid) was obtained as a sodium salt.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.10-3.90 (16H, m), 6.40-6.48 (1H, m),

6.95 (1H, d, J=2.9Hz), 7.19 (1H, dd, J=8.8, 2.0Hz), 7.41 (3H, m),
7.64 (1H, d, J=2.5Hz), 8.40 (2H, m).

[Example A-258] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-
[(piperidin-1-yl)carbonylmethyl]-1-[[4-(pyridin-4-yl)-3-
5 cyclohexen-1-yl]carbonyl]piperazine

In the same manner as in Example A-4, the title
compound was obtained.

¹H-NMR (CDCl₃) δ: 1.61-3.82 (24H, m), 4.65-4.93 (2H, m), 6.96-
7.68 (5H, m), 8.02 (1H, s), 8.51 (2H, m).

10 [Example A-259] 4-[4-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-
[(piperidin-1-yl)carbonylmethyl]piperazin-1-yl]carbonyl]-1-
cyclohexen-1-yl]pyridine N-oxide

In the same manner as in Example A-6, the title
compound was obtained.

15 ¹H-NMR (DMSO-d₆) δ: 1.63-4.94 (26H, m), 6.28 (1H, m),
6.99 (1H, m), 7.18-7.40 (4H, m), 7.65 (1H, d, J=15.4Hz),
8.13 (1H, d, J=4.9Hz).

MS (FAB) m/z: 626 [(M+H)⁺, Cl³⁵].

[Example A-260] 1-[(E)-4-Chloro-2-
20 methoxystyryl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-
yl]carbonyl]piperazine hydrochloride

In the same manner as in Example A-105, the title
compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.07 (2H, br), 3.24 (2H, br), 3.39 (2H, br),
25 3.82 (2H, br), 3.92 (2H, s), 7.10 (1H, dd, J=8.3, 1.5Hz),

7.23 (1H, d, J=1.5 Hz), 7.29 (1H, d, J=15.6 Hz),
7.56 (1H, d, J=15.6 Hz), 7.84 (1H, d, J=8.3 Hz),
8.34 (2H, d, J=6.1 Hz), 8.98 (2H, d, J=6.1 Hz), 9.46 (2H, s).
MS (FAB) m/z: 500 [(M+H)⁺, Cl³⁵], 502 [(M+H)⁺, Cl³⁷].

5 [Example A-261] 1-[((E)-4-Chloro-2-hydroxystyryl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine hydrochloride

In methylene chloride (18 ml) was dissolved 1-[((E)-4-chloro-2-methoxystyryl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine (366 mg), followed by
10 the addition of boron tribromide (a 1.0 mole solution, methylene chloride) at -78°C in an argon atmosphere. The resulting mixture was stirred at -78°C for 0.5 hour and 0°C for 2 hours. The reaction mixture was distilled under
15 reduced pressure. After a saturated aqueous solution of sodium bicarbonate and water were added to the residue and the insoluble matter was filtered off, methylene chloride was added for extraction. The organic layer was washed with saturated saline, dried over anhydrous sodium sulfate
20 and distilled under reduced pressure to remove the solvent. The residue was subjected to column chromatography (10% methanol - methylene chloride) using as a carrier silica gel and then chromatography on a silica gel column (methylene chloride ~ 5% methanol - methylene chloride),
25 whereby a crudely purified product (146 mg) was obtained. A portion (81.0 mg) of the product was dissolved in

tetrahydrofuran. To the resulting solution was added 1N aqueous hydrochloric acid in ethanol. The resulting mixture was solidified, followed by collection by filtration. The resulting solid was then dissolved in methanol. After filtration of the resulting solution, water was added. The solvent was distilled off under reduced pressure, whereby the title compound (68.5 g) was obtained as colorless powder.

¹H-NMR (DMSO-d₆) δ: 3.00-3.10 (2H, m), 3.20-3.25 (2H, m), 3.35-3.45 (2H, m), 3.80-3.85 (2H, m), 6.94 (1H, d, J=8.3 Hz), 7.05 (1H, s), 7.24 (1H, d, J=15.6 Hz), 7.55 (1H, d, J=15.6 Hz), 7.74 (1H, d, J=8.3 Hz), 8.36 (2H, br s), 8.95-9.05 (2H, m), 9.47 (2H, s), 11.10 (1H, br s).

MS (FAB) m/z: 486 [(M+H)⁺, Cl³⁵], 488 [(M+H)⁺, Cl³⁷].

[Example A-262] 4-[2-[[4-[(E)-4-Chloro-2-hydroxystyryl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example A-105, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.00-3.10 (2H, m), 3.15-3.25 (2H, m), 3.35-3.40 (2H, m), 3.75-3.85 (2H, m), 6.90-7.00 (2H, m), 7.23 (1H, d, J=15.6 Hz), 7.54 (1H, d, J=15.6 Hz), 7.74 (1H, d, J=8.3 Hz), 7.97 (2H, d, J=7.8 Hz), 8.45-8.50 (2H, m), 9.32 (2H, s), 10.95 (1H, br s).

MS (FAB) m/z: 502 [(M+H)⁺, Cl³⁵], 504 [(M+H)⁺, Cl³⁷].

[Example A-263] 2,cis-6-Bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

In the same manner as in Example A-105, the title
5 compound was obtained.

¹H-NMR (CDCl₃) δ: 2.50-2.80 (3H,m), 2.95-3.05 (2H,m), 3.10-
3.20 (1H,m), 3.65-3.75 (1H,m), 3.68 (3H,s), 3.75 (3H,s), 4.00-
4.10 (1H,m), 4.15-4.25 (1H,m), 5.15-5.25 (1H,m), 7.40-
7.50 (2H,m), 7.55-7.60 (1H,m), 7.70-7.75 (1H,m), 7.90-
10 7.95 (3H,m), 8.30 (1H,s), 8.75-8.85 (2H,m), 8.96 (2H,s).

[Example A-264] 2,cis-6-Bis(carbamoylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

In tetrahydrofuran (10 ml) and methanol (5 ml) were
15 dissolved 2,cis-6-bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine (372 mg), followed by the
dropwise addition of a mixture of sodium hydroxide (310 ml)
and water (1.6 ml) under ice cooling. The resulting
20 mixture was stirred at room temperature for 23.5 hours.
After concentrated hydrochloric acid was added to the
reaction mixture to make it acidic, the solvent was
distilled off under reduced pressure. The residue was
suspended in N,N-dimethylformamide (15 ml), followed by the
25 addition of di-tert-butyl dicarbonate (665 mg), pyridine
(290 μl) and ammonium bicarbonate (304 mg) under ice

cooling. The resulting mixture was stirred at room temperature for 19 hours. After completion of the the stirring, the solvent was distilled off under reduced pressure. The residue was subjected to chromatography on a silica gel column (methylene chloride ~ 20% methanol - methylene chloride), whereby a crudely purified product (182 mg) was obtained. A 62.3 mg portion of the resulting product was subjected to chromatography on a silica gel column (methylene chloride ~ 15% methanol - methylene chloride). The solvent was then distilled off under reduced pressure. Ethyl acetate was added to the residue to solidify the same, whereby the title compound (23 mg) was obtained as pale yellow powder.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.25-2.35 (1H,m), 2.40-2.60 (3H,m), 2.80-3.00 (2H,m), 3.50-3.60 (1H,m), 3.8-3.95 (2H,m), 4.90-5.00 (1H,m), 6.90 (1H,br s), 7.06 (1H,br s), 7.45 (1H,br s), 7.53 (1H,br s), 7.70-7.75 (1H,m), 7.75-7.85 (1H,m), 7.85-7.95 (2H,m), 8.17 (1H,d,J=8.8Hz), 8.25-8.35 (2H,m), 8.51 (1H,s), 8.70-8.75 (1H,m), 9.31 (2H,s).

MS (FAB) m/z : 608 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 610 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Example A-265] 4-[2-[[2,cis-6-Bis(carbamoylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.25-2.35 (1H,m), 2.40-2.60 (3H,m), 2.80-3.00 (2H,m), 3.55-3.60 (1H,m), 3.85-3.95 (2H,m), 4.90-5.00 (1H,m), 6.89 (1H,br s), 7.06 (1H,br s), 7.43 (1H,br s), 7.51 (1H,br s), 7.70-7.75 (1H,m), 7.75-7.85 (1H,m),
 5 7.97 (2H,d,J=7.3Hz), 8.16 (1H,d,J=8.8Hz), 8.20-8.40 (4H,m), 8.51 (1H,s), 9.29 (2H,s).

MS (FAB) m/z: 624 [(M+H)⁺, Cl³⁵], 626 [(M+H)⁺, Cl³⁷].

[Example A-266] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-(methoxycarbonylmethyl)-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine
 10

In the same manner as in Example A-105, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.45-3.30 (6H,m), 3.50-5.40 (6H,m), 3.67, 3.74 (3H,each s), 7.45-7.50 (2H,m), 7.55-7.65 (1H,m), 7.70-7.80 (1H,m), 7.90-7.95 (3H,m), 8.29 (1H,br s),
 15 8.78 (2H,d,J=5.4Hz), 8.99, 9.00 (2H,each s).

[Example A-267] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[(morpholin-4-yl)carbonyl]methyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine hydrochloride

20 In tetrahydrofuran (10 ml) and methanol (5.0 ml) was dissolved 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-(methoxycarbonylmethyl)-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine (583 mg). Under ice cooling, a mixture of sodium hydroxide (200 mg) and water (1.0 ml) was added.
 25 dropwise to the resulting solution under ice cooling, followed by stirring at room temperature for 5 hours.

Under ice cooling, concentrated hydrochloric acid (420 μ l) was added to the reaction mixture to make it weakly acidic. The reaction mixture was then distilled under reduced pressure. To the residue were added morpholine (102 μ l),
5 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (239 mg) and 1-hydroxybenzotriazole hydrate (159 mg). The resulting mixture was dissolved in N,N-dimethylformamide (60 ml) and methylene chloride (30 ml).
Diisopropylethylamine (760 μ l) was added dropwise to the
10 resulting solution under ice cooling, followed by stirring at room temperature for 12.5 hours. The reaction mixture was distilled under reduced pressure. A 100% aqueous solution of citric acid was added to the residue and it was extracted with methylene chloride. The organic layer was
15 washed with a saturated aqueous solution of sodium bicarbonate and saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to column chromatography (10% methanol - methylene
20 chloride) using as a carrier silica gel, followed by crystallization from methylene chloride - tetrahydrofuran, whereby a crudely purified product (349 mg) was obtained. A portion (161 mg) of the product was dissolved in
25 methylene chloride - methanol. To the resulting solution was added 1N aqueous hydrochloride in ethanol (260 μ l) and the mixture was concentrated to dryness. Ethyl acetate was

added to the concentrate and the solid thus obtained was collected by filtration, washed with ethyl acetate and dried, whereby the title compound (117 mg) was obtained as colorless powder.

5 ^1H -NMR (CDCl_3) δ : 2.25-5.15 (17H,m), 7.70-7.75 (1H,m), 7.82 (1H,d,J=8.8Hz), 8.15-8.30 (5H,m), 8.51 (1H,br s), 8.90-9.00 (2H,m), 9.35-9.45 (2H,m).

MS (FAB) m/z : 621 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 623 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Example A-268] 2,cis-6-Bis[(N-methylcarbamoyl)methyl]-4-
10 [(6-chloronaphthalen-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine hydrochloride

In the same manner as in Example A-264, the title compound was obtained.

15 ^1H -NMR ($\text{DMSO}-d_6$) δ : 2.20-2.70 (10H,m), 2.70-2.90 (2H,m), 3.40-4.10 (3H,m), 4.90-5.00 (1H,m), 7.73 (1H,d,J=7.8Hz), 7.81 (1H,d,J=7.8Hz), 7.94 (1H,d,J=4.4Hz), 8.01 (1H,d,J=4.4Hz), 8.17 (1H,d,J=8.3Hz), 8.20-8.40 (4H,m), 8.52 (1H,s), 8.98 (2H,d,J=5.9Hz), 9.43 (2H,s).

MS (FAB) m/z : 636 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 638 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

20 [Example A-269] 2,cis-6-Bis[(N,N-dimethylcarbamoyl)methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine hydrochloride

25 In the same manner as in Example A-264, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.50-3.10 (6H,m), 2.73 (3H,s),
 2.86 (3H,s), 2.97 (3H,s), 3.04 (3H,s), 3.53 (1H,d,J=11.7Hz),
 3.84 (1H,d,J=12.2Hz), 3.99 (1H,d,J=9.8Hz),
 5.02 (1H,d,J=10.8Hz), 7.71 (1H,dd,J=9.0,2.2Hz),
 5 7.79 (1H,dd,J=8.5,1.7Hz), 8.17 (1H,d,J=8.8Hz), 8.20-
 8.35 (4H,m), 8.51 (1H,s), 8.90-8.95 (2H,m), 9.35-9.45 (2H,m).
 MS (FAB) m/z: 664 [(M+H)⁺, Cl³⁵], 666 [(M+H)⁺, Cl³⁷].

[Example A-270] 4-[2-[[4-[(6-Chloronaphthalen-2-
 yl)sulfonyl]-2-[(morpholin-4-yl)carbonyl]methyl]piperazin-
 10 1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example A-6, the title
 compound was obtained.

¹H-NMR (CDCl₃) δ: 2.25-5.15 (17H,m), 7.70-7.75 (1H,m), 7.80-
 7.85 (1H,m), 7.90-8.00 (2H,m), 8.18 (1H,d,J=8.8Hz), 8.20-
 15 8.30 (2H,m), 8.30-8.40 (2H,m), 8.49 (1H,br s),
 9.26 (2H,d,J=7.8Hz).

MS (FAB) m/z: 637 [(M+H)⁺, Cl³⁵], 639 [(M+H)⁺, Cl³⁷].

[Example A-271] 4-[2-[[2,cis-6-Bis(N,N-
 dimethylcarbamoylmethyl)-4-(6-chloronaphthalen-2-
 20 ylsulfonyl)piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine
 N-oxide

In the same manner as in Example A-6, the title
 compound was obtained.

¹H-NMR (CDCl₃) δ: 2.50-3.30 (6H,m), 2.91 (3H,m), 3.00 (3H,m),
 25 3.08 (3H,m), 3.12 (3H,m), 3.70 (1H,d,J=12.2Hz),

4.16 (1H, d, J=12.7Hz), 4.37 (1H, d, J=10.7Hz), 5.20-5.30 (1H, m),
 7.50 (2H, d, J=7.3Hz), 7.57 (1H, dd, J=8.8, 2.0Hz),
 7.72 (1H, dd, J=8.6, 1.7Hz), 7.85-7.95 (3H, m), 8.25-8.35 (3H, m),
 8.91 (2H, s).

5 MS (FAB) m/z: 680 [(M+H)⁺, Cl³⁵], 682 [(M+H)⁺, Cl³⁷].

[Example A-272] 4-[2-[[2, cis-6-Bis(N-methylcarbamoylmethyl)-4-(6-chloronaphthalen-2-ylsulfonyl)piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

10 In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (CD₃OD) δ: 2.50-2.80 (4H, m), 2.66 (3H, s), 2.78 (3H, s),
 2.90-3.00 (2H, m), 3.64 (1H, d, J=12.7Hz), 4.01 (1H, d, J=12.2Hz),
 4.20 (1H, d, J=9.8Hz), 5.10-5.15 (1H, m),
 15 7.62 (1H, dd, J=8.8, 2.0Hz), 7.78 (1H, dd, J=8.8, 1.5Hz),
 7.97 (2H, d, J=7.3Hz), 8.00-8.10 (3H, m), 8.35-8.45 (3H, m),
 9.20 (2H, s).

MS (FAB) m/z: 652 [(M+H)⁺, Cl³⁵], 654 [(M+H)⁺, Cl³⁷].

20 [Example A-273] 2-[2-(tert-Butyldiphenylsilyloxy)ethyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

In the same manner as in Example A-105, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 0.84, 1.09 (9H, each s), 2.10-2.20 (2H, m),
 25 2.35-2.65 (2H, m), 3.15-5.25 (7H, m), 7.10-7.80 (14H, m), 7.85-

8.00 (3H,m), 8.20-8.30 (1H,m), 8.65-9.00 (4H,m).

MS (FAB) m/z: 776 [(M+H)⁺, Cl³⁵], 778 [(M+H)⁺, Cl³⁷].

[Example A-274] 4-(6-Chloronaphthalen-2-ylsulfonyl)-2-(2-hydroxyethyl)-1-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine hydrochloride

In pyridine (6.0 ml) was dissolved 2-[(tert-butyl diphenylsilyloxy)methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine (150 mg). A hydrogen fluoride - pyridine complex (2.0 ml) was added dropwise to the resulting solution under ice cooling, followed by stirring at 0°C for 1.5 hours. Ethyl acetate (40 ml) was added to the reaction mixture to dilute it. Then, the diluted mixture was poured into ice. The resulting mixture was extracted. The organic layer was washed with saturated saline, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to column chromatography (5% methanol - methylene chloride ~ 10% methanol - methylene chloride) using as a carrier silica gel, whereby a crudely purified product (97.9 mg) was obtained. The resulting product was dissolved in methylene chloride, followed by the addition of 1N hydrochloric acid in ethanol (182 µl) for solidification. Tetrahydrofuran was added to the residue to solidify the same, whereby the title compound (62.7 mg) was obtained as colorless crystalline powder.

¹H-NMR (DMSO-d₆) δ: 2.20-5.20 (9H,m), 6.90-7.05 (1H,m), 7.50-7.60 (2H,m), 7.70-7.90 (2H,m), 8.00-8.10 (1H,m), 8.19 (1H,d,J=8.3Hz), 8.25-8.35 (2H,m), 8.40-8.50 (3H,m), 9.00 (2H,d,J=5.9Hz).

5 MS (FAB) m/z: 538 [(M+H)⁺, Cl³⁵], 540 [(M+H)⁺, Cl³⁷].

[Example A-275] 2-cis,6-Bis(methoxycarbonylmethyl)-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

10 In the same manner as in Example A-105, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.70-2.85 (3H,m), 2.95-3.15 (3H,m), 3.65-3.75 (1H,m), 3.67 (3H,s), 3.75 (3H,s), 4.02 (1H,d,J=12.7Hz), 4.29 (1H,d,J=9.8Hz), 5.25-5.35 (1H,m), 7.45-7.55 (3H,m), 7.75-7.90 (3H,m), 8.75-8.85 (2H,m), 8.98 (2H,s).

15 MS (FAB) m/z: 644 [(M+H)⁺, Cl³⁵], 646 [(M+H)⁺, Cl³⁷].

[Example A-276] 2-[(tert-Butyldiphenylsilyloxy)methyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine hydrochloride

20 In the same manner as in Example A-105, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 0.95 (9H x 0.5,s), 1.04 (9H x 0.5,s), 2.50-3.60 (4H,m), 3.70-3.90 (2H,m), 3.95-4.10 (2H,m), 4.45-5.00 (1H,m), 7.30-7.55 (7H,m), 7.55-7.65 (2H,m), 7.70-7.75 (2H,m), 8.05-8.15 (2H,m), 8.25-8.40 (3H,m), 8.95-9.05 (2H,m), 9.25-9.35 (1H,m), 9.40-9.45 (1H,m).

25

MS (FAB) m/z : 768 $[(M+H)^+, Cl^{35}]$, 770 $[(M+H)^+, Cl^{37}]$.

[Example A-277] 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(hydroxymethyl)-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine hydrochloride

5 In the same manner as in Example A-274, the title compound was obtained.

1H -NMR (DMSO- d_6) δ : 2.40-2.70 (2H,m), 3.10-4.00 (6H,m), 4.45-4.75 (1H,m), 7.55-7.65 (1H,m), 8.05-8.15 (2H,m), 8.35 (1H,s), 8.40-8.45 (2H,m), 9.03 (2H,d,J=4.4Hz), 9.46 (2H,s).

10 MS (FAB) m/z : 530 $[(M+H)^+, Cl^{35}]$, 532 $[(M+H)^+, Cl^{37}]$.

[Example A-278] 2,cis-6-Bis[(N,N-dimethylcarbamoyl)methyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine hydrochloride

15 In the same manner as in Example A-264, the title compound was obtained.

1H -NMR (DMSO- d_6) δ : 2.40-3.80 (7H,m), 2.74 (3H,s), 2.87 (3H,s), 2.98 (3H,s), 3.05 (3H,s), 3.83 (1H,d,J=12Hz), 4.00-4.05 (1H,m), 5.06 (1H,d,J=8.7Hz),

20 7.58 (1H,dd,J=8.8,2.0Hz), 8.07 (1H,d,J=8.8Hz), 8.10-8.20 (3H,m), 8.35 (1H,s), 8.87 (2H,d,J=5.4Hz), 9.39 (2H,s).

MS (FAB) m/z : 670 $[(M+H)^+, Cl^{35}]$, 672 $[(M+H)^+, Cl^{37}]$.

[Example A-279] 4-[2-[[2,cis-6-Bis[(N,N-dimethylcarbamoyl)methyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine

25

N-oxide

In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.40-3.10 (4H,m), 2.74 (3H,s),
 2.87 (3H,s), 3.04 (3H,s), 3.33 (3H,s), 3.40-3.50 (2H,m),
 3.52 (1H,d,J=11.7Hz), 3.82 (1H,d,J=12.7Hz),
 4.03 (1H,d,J=6.8Hz), 5.05 (1H,d,J=10.3Hz),
 7.59 (1H,dd,J=8.8,2.0Hz), 7.99 (2H,d,J=7.3Hz),
 8.07 (1H,d,J=8.3Hz), 8.12 (1H,s), 8.30-8.40 (3H,m),
 9.30 (2H,s).

MS (FAB) m/z: 686 [(M+H)⁺, Cl³⁵], 688 [(M+H)⁺, Cl³⁷].

[Example A-280] 4-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(hydroxymethyl)piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.40-2.70 (2H,m), 3.10-4.00 (6H,m),
 4.47 (1H,d,J=13.7Hz), 4.67 (1H,br s), 4.89 (1H,t,J=5.4Hz),
 5.16 (1H,t,J=5.4Hz), 7.55-7.65 (1H,m), 7.90-8.00 (2H,m), 8.05-
 8.15 (2H,m), 8.30-8.40 (3H,m), 9.30 (2H,s).

MS (FAB) m/z: 546 [(M+H)⁺, Cl³⁵], 548 [(M+H)⁺, Cl³⁷].

[Example A-281] 2-[2-(tert-Butyldiphenylsilyloxy)ethyl]-4-[[6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine hydrochloride

In the same manner as in Example A-105, the title

compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 0.79, 1.02 (9H, each s), 1.70-5.10 (11H, m), 7.35-7.70 (12H, m), 8.05-8.40 (4H, m), 8.90-9.05 (2H, m), 9.35, 9.45 (2H, each s).

5 MS (FAB) m/z : 782 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 784 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Example A-282] 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(2-hydroxyethyl)-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine hydrochloride

10 In the same manner as in Example A-274, the title compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.80-2.00 (2H, m), 2.40-3.90 (9H, m), 4.45-5.00 (1H, m), 7.55-7.65 (1H, m), 8.05-8.15 (2H, m), 8.35-8.45 (3H, m), 9.01 (2H, d, $J=7.8\text{Hz}$), 9.45 (2H, d, $J=2.4\text{Hz}$).

MS (FAB) m/z : 544 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 546 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

15 [Example A-283] 2-[2-(tert-Butyldiphenylsilyloxy)ethyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[5-(pyridin-2-yl)pyrimidin-2-yl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

20 $^1\text{H-NMR}$ (DMSO-d_6) δ : 0.82, 1.09 (9H, each s), 2.05-2.20 (2H, m), 2.55-2.80 (2H, m), 3.15-4.25 (6H, m), 4.70-5.30 (1H, m), 7.10-7.55 (11H, m), 7.70-7.90 (6H, m), 8.70-8.80 (1H, m), 9.22, 9.34 (2H, each s).

MS (FAB) m/z : 782 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 784 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

25 [Example A-284] 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-

2-(2-hydroxyethyl)-1-[5-(pyridin-2-yl)pyrimidin-2-yl]piperazine hydrochloride

In the same manner as in Example A-274, the title compound was obtained.

5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.80-2.00 (2H,m), 2.40-3.90 (9H,m), 4.45-5.00 (1H,m), 7.50-7.65 (2H,m), 8.00-8.15 (3H,m), 8.15-8.25 (1H,m), 8.34 (1H,s), 8.77 (1H,d,J=4.4Hz), 9.48 (2H,s).
MS (FAB) m/z: 544 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 546 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Example A-285] 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-
10 2-[(methoxycarbonyl)methyl]-1-[5-(pyridin-2-yl)pyrimidin-2-yl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.60-3.30 (5H,m), 3.50-5.45 (7H,m), 7.20-
15 7.55 (2H,m), 7.70-7.90 (5H,m), 8.76 (1H,d,J=4.9Hz), 8.76 (2H,d,J=2.4Hz).
MS (FAB) m/z: 572 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 574 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Example A-286] 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(methoxycarbonyl)methyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide
20

In the same manner as in Example A-6, the title compound was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.60-3.30 (4H,m), 3.50-5.40 (5H,m), 3.67, 3.74 (3H,each s), 7.30-7.55 (4H,m), 7.70-7.90 (3H,m), 8.30-
25 8.40 (1H,m), 9.29 (2H,d,J=12.2Hz).

MS (FAB) m/z: 572 [(M+H)⁺, Cl³⁵], 574 [(M+H)⁺, Cl³⁷].

[Example A-287] 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N,N-dimethylcarbamoyl)methyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

5 In the same manner as in Example A-267, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.30-2.80 (3H,m), 2.74 (3H,s),
2.85 (3H,s), 2.92 (3H,s), 3.01 (3H,s), 3.10-4.15 (5H,m), 4.50-
5.15 (1H,m), 7.45-7.65 (3H,m), 7.85-7.95 (1H,m), 8.05-
10 8.15 (2H,m), 8.34 (1H,s), 8.40-8.45 (1H,m), 9.35 (2H,s).

MS (FAB) m/z: 601 [(M+H)⁺, Cl³⁵], 603 [(M+H)⁺, Cl³⁷].

[Example A-288] 2-[2-[[2-(2-tert-
Butyldiphenylsilyloxyethyl)-4-[(6-chlorobenzo[b]thien-2-
yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine
15 N-oxide

In the same manner as in Example A-6, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 0.80-1.10 (9H,m), 2.00-2.20 (2H,m), 2.50-
2.80 (2H,m), 3.10-4.30 (6H,m), 4.65-5.30 (1H,m), 7.05-
20 7.90 (17H,m), 8.30-8.40 (1H,m), 9.10-9.30 (2H,m).

MS (FAB) m/z: 798 [(M+H)⁺, Cl³⁵], 800 [(M+H)⁺, Cl³⁷].

[Example A-289] 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-
yl)sulfonyl]-2-(2-hydroxyethyl)piperazin-1-
yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

25 In the same manner as in Example A-274, the title

compound was obtained.

¹H-NMR (CDCl₃) δ: 1.80-2.05 (1H,m), 2.25-2.45 (1H,m), 2.60-2.95 (2H,m), 3.00-4.20 (7H,m), 4.70-5.10 (1H,m), 7.40-7.55 (4H,m), 7.70-7.90 (3H,m), 8.30-8.40 (1H,m), 9.30 (2H,s).

5 MS (FAB) m/z: 560 [(M+H)⁺, Cl³⁵], 562 [(M+H)⁺, Cl³⁷].

[Example A-290] 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(pyrrolidin-1-yl)carbonyl]methyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

10 In the same manner as in Example A-267, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.70-1.90 (4H,m), 2.30-4.20 (12H,m), 4.50-5.20 (1H,m), 7.45-7.65 (3H,m), 7.85-7.90 (1H,m), 8.05-8.15 (2H,m), 8.34 (1H,s), 8.43 (1H,d,J=6.3Hz), 9.35 (2H,s).

15 MS (FAB) m/z: 627 [(M+H)⁺, Cl³⁵], 629 [(M+H)⁺, Cl³⁷].

[Example A-291] 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

20 In the same manner as in Example A-267, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.30-2.90 (5H,m), 3.15-4.25 (6H,m), 4.50-5.20 (1H,m), 7.45-7.60 (3H,m), 7.85-8.00 (1H,m), 8.05-8.15 (2H,m), 8.34 (1H,s), 8.43 (1H,d,J=6.3Hz), 9.35 (2H,d,J=4.9Hz).

25 MS (FAB) m/z: 587 [(M+H)⁺, Cl³⁵], 589 [(M+H)⁺, Cl³⁷].

[Example A-292] 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(thiomorpholin-4-yl)carbonyl]methyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

5 In the same manner as in Example A-267, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.50-2.90 (7H,m), 3.10-4.85 (9H,m), 4.45-5.45 (1H,m), 7.35-7.55 (4H,m), 7.75-7.90 (3H,m), 8.30-8.40 (1H,m), 9.30 (2H,d,J=10.5Hz).

10 MS (FAB) m/z: 659 [(M+H)⁺, Cl³⁵], 661 [(M+H)⁺, Cl³⁷].

[Example A-293] 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N-cyclopropylcarbamoyl)methyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

15 In the same manner as in Example A-267, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 0.50-0.90 (4H,m), 2.60-6.20 (11H,m), 7.35-7.55 (4H,m), 7.70-7.90 (3H,m), 8.30-8.40 (1H,m), 9.25-9.35 (2H,m).

MS (FAB) m/z: 613 [(M+H)⁺, Cl³⁵], 615 [(M+H)⁺, Cl³⁷].

20 [Example A-294] 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(morpholin-4-yl)carbonyl]methyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example A-267, the title compound was obtained.

25 ¹H-NMR (CDCl₃) δ: 2.55-2.85 (4H,m), 3.10-5.45 (13H,m), 7.35-

7.55 (4H,m), 7.70-7.90 (3H,m), 8.30-8.40 (1H,m), 9.25-9.35 (2H,m).

MS (FAB) m/z: 643 [(M+H)⁺, Cl³⁵], 645 [(M+H)⁺, Cl³⁷].

[Example A-295] 2-[2-[[2-[(N-Benzylcarbamoyl)methyl]-4-
5 [(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example A-267, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.65-2.85 (3H,m), 2.95-5.45 (8H,m), 6.10-
10 6.30 (1H,m), 7.25-7.55 (9H,m), 7.70-7.90 (3H,m), 8.30-8.40 (1H,m), 9.25-9.30 (2H,m).

MS (FAB) m/z: 663 [(M+H)⁺, Cl³⁵], 665 [(M+H)⁺, Cl³⁷].

[Example A-296] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[4-methyl-2-(pyridin-4-yl)thiazol-5-yl]piperazine

15 In the same manner as in Example A-4, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.35 (3H,s), 3.00-3.15 (4H,br), 3.55-3.73 (4H,br), 7.01 (1H,s), 7.30 (1H,dd, J=8.8, 2.2Hz),
7.49 (1H,d, J=8.8Hz), 7.765 (1H,d, J=2.0Hz),
20 7.82 (2H,d, J=6.2Hz), 8.69 (2H,d, J=6.2Hz).

MS (FAB) m/z: 502 [(M+H)⁺, Cl³⁵], 504 [(M+H)⁺, Cl³⁷].

[Example A-297] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[[5-(pyridin-4-yl)thiazol-2-yl]carbonyl]-2-[(pyrrolidin-1-yl)carbonylmethyl]piperazine

25 In the same manner as in Example A-66, the title

compound was obtained.

¹H-NMR (CDCl₃) δ: 1.85-2.05 (4H,m), 2.50-3.30 (5H,m), 3.40-3.60 (4H,m), 3.81, 3.90, 4.03, 4.23, 4.64, 5.62 (3H, each br d, J=12.5Hz), 5.15-6.21 (1H,m), 6.99 (1H,s), 7.25-7.50 (4H,m), 7.64 (1H,d, J=5.6Hz), 8.60-8.70 (3H,m), 10.38, 10.95 (1H, each s).

FAB-MS m/z: 599 [(M+H)⁺, Cl³⁵], 601 [(M+H)⁺, Cl³⁷].

[Example A-298] 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(pyrrolidin-1-yl)carbonylmethyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine N-oxide

In the same manner as in Example A-4, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.65-1.90 (4H,m), 2.30-3.50 (9H,m), 3.50-3.88 (2H,m), 4.41, 5.40 (1H, each br d, J=12.5Hz), 5.02-5.95 (1H,m), 7.02 (1H,s), 7.31 (1H,dd, J=8.8, 2.0Hz), 7.48 (1H,d, J=8.8Hz), 7.75-7.83 (3H,m), 8.26 (2H,d, J=7.1Hz), 8.45, 8.49 (1H, each s), 12.42 (1H, br s).

MS (FAB) m/z: 615 [(M+H)⁺, Cl³⁵], 617 [(M+H)⁺, Cl³⁷].

[Example A-299] 2-[(N-Benzylcarbamoyl)methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[[5-(pyridin-4-yl)thiazol-2-yl]carbonyl]piperazine

In the same manner as in Example A-66, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.60-3.06 (4H,m), 3.12-3.57 (1H,m), 3.78-3.95 (1H,m), 3.98-4.12 (1H,m), 4.38-4.56 (2H,m), 4.57-

6.01 (2H, m), 6.47, 6.58 (1H, each br s), 6.97 (1H, s), 7.25-7.52 (8H, m), 7.65 (2H, d, J=6.6 Hz), 8.64-8.71 (3H, m), 10.24 (1H, s).

FAB-MS m/z: 635 [(M+H)⁺, Cl³⁵], 637 [(M+H)⁺, Cl³⁷].

5 [Example A-300] 4-[2-[[2-(N-Benzylcarbamoyl)methyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine N-oxide

In the same manner as in Example A-4, the title compound was obtained.

10 ¹H-NMR (DMSO-d₆) δ: 2.30-2.92 (3H, m), 3.20-3.63 (2H, m), 3.65-3.85 (2H, m), 4.15-4.35 (2H, m), 4.41, 5.41 (1H, each br d, J=13.5 Hz), 5.15, 5.98 (1H, each br s), 7.02 (1H, s), 7.15-7.33 (6H, m), 7.48 (1H, d, J=8.6 Hz), 7.73-7.81 (3H, m), 8.26 (2H, d, J=6.6 Hz), 8.38-8.60 (2H, m), 12.41 (1H, br s).

15 MS (FAB) m/z: 651 [(M+H)⁺, Cl³⁵], 653 [(M+H)⁺, Cl³⁷].

[Example A-301] 1-[4-[2-(2-Aminoethyl)pyridin-4-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Example A-7, the title compound was obtained.

20 ¹H-NMR (DMSO-d₆) δ: 3.08 (4H, s), 3.23 (2H, br), 3.30 (2H, br), 3.45 (2H, br), 3.73 (2H, br), 7.52 (2H, d, J=8.3 Hz), 7.74 (1H, dd, J=5.4, 2.0 Hz), 7.80-7.87 (5H, m), 8.06 (2H, br), 8.19 (1H, d, J=8.8 Hz), 8.25-8.31 (2H, m), 8.51 (1H, br s), 8.69 (1H, d, J=4.4 Hz).

25 MS (FAB) m/z: 535 [(M+H)⁺, Cl³⁵], 537 [(M+H)⁺, Cl³⁷].

Elementary analysis for $C_{28}H_{27}ClN_4O_3S \cdot 1.85HCl \cdot 1.4H_2O$

Calculated: C, 53.57; H, 5.08; Cl, 16.10; N, 8.93; S, 5.11.

Found: C, 53.39; H, 5.06; Cl, 15.99; N, 8.81; S, 5.08.

[Example A-302] 1-[[5(6)-Chloroimidazol-2-yl]sulfonyl]-4-
5 [4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

1-[[5(6)-Chlorobenzimidazol-2-yl]sulfonyl]piperazine
(507 mg), 1-hydroxybenzotriazole (220 mg), N-
methylmorpholine (480 μ l) and 1-ethyl-3-(3-
dimethylaminopropyl)-carbodiimide (309 mg) were
10 successively added to the mixture of 4-[(pyridin-4-
yl)benzoic acid (314 mg), dichloromethane (5.0 ml) and N,N-
dimethylformamide (2.0 ml), stirred at room temperature for
5 hours. The mixture was diluted with dichloromethane, and
then divided into two layers by adding a saturated sodium
15 chloride solution. The organic layer was washed with a
saturated sodium chloride solution, dried over sodium
sulfate, and concentrated under reduced pressure. The
obtained product was purified by chromatography on a silica
gel column (dichloromethane:methanol = 15:1). After
20 dichloromethane was removed from the mixture of
dichloromethane and methanol under reduced pressure, 1-
[[5(6)-chloroimidazol-2-yl]sulfonyl]-4-[4-(pyridin-4-
yl)benzoyl]piperazine (396 mg) was obtained as precipitated
powder by filtration. 140 mg of this obtained compound was
25 concentrated by adding 1N aqueous hydrochloride in ethanol
(3 ml) and ethanol (3 ml), and dried, whereby the title

compound (152 mg) was obtained as colorless amorphous.

IR (KBr) cm^{-1} 1631, 1431, 1365, 1282, 1155.

^1H -NMR (DMSO-d_6) δ , 3.30-4.00 (8H, br), 7.43 (1H, d, J = 8.8, 2.0 Hz), 7.62 (2H, d, J = 7.8 Hz), 7.75 (1H, d, J = 8.8 Hz), 7.80 (1H, s), 8.07 (2H, d, J = 8.8 Hz), 8.38 (2H, d, J = 5.9 Hz), 8.97 (2H, d, J = 5.9 Hz).

MS (FAB) m/z 482 $[(M + H)^+, \text{Cl}^{35}]$, 484 $[(M + H)^+, \text{Cl}^{37}]$.

[Example A-303] 4-[4-[[5(6)-chlorobenzimidazol-2-yl]sulfonyl]piperazin-1-yl]carbonylphenyl]pyridine N-oxide

Metachloroperbenzoic acid (0°C; 121 mg) was added to the mixture of 1-[[5(6)-chloroimidazol-2-yl]sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine (191 mg) obtained by Example A-302, N,N -dimethylformamide (5.0 ml) and chloroform (15 ml) at a temperature of 0°C, and stirred at a temperature of 0°C for 3 hours, thereto was added dichloromethane (50 ml), followed by stirring at room temperature for 64 hours. The mixture was divided into two layers by adding a small quantity of sodium thiosulfate solution, and saturated sodium chloride solution. The organic layer was washed with a saturated sodium hydrogencarbonate solution and a saturated sodium chloride solution, dried over sodium sulfate, and concentrated under reduced pressure. The obtained product was purified by chromatography on a silica gel column

(dichloromethane:methanol = 20:1). The mixture of

dichloromethane and methanol was concentrated under reduced pressure, filtered and dried to obtain solid. Thus, the title compound (141 mg) was obtained as colorless amorphous.

5 IR (KBr) cm^{-1} 1645, 1433, 1371, 1248, 1180, 966, 933.

^1H -NMR (DMSO- d_6) δ , 3.30-3.85 (8H, br), 7.41 (1H, dd, J = 8.8, 2.0 Hz), 7.49 (2H, d, J = 7.8 Hz), 7.68-7.83 (2H, br), 7.80 (2H, d, J = 6.8 Hz), 7.83 (2H, d, J = 7.8 Hz), 8.27 (2H, d, J = 6.8 Hz).

10 MS (FAB) m/z 498 $[(M + H)^+, \text{Cl}^{35}]$, 500 $[(M + H)^+, \text{Cl}^{37}]$.

[Example B-1] 1-[[[(6RS)-6-Aminomethyl-5,6,7,8-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In saturated aqueous hydrochloric acid in ethanol (5
15 ml), 1-[[[(6RS)-6-(N-tert-butoxycarbonylaminomethyl)-5,6,7,8-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine (0.22 g) was dissolved, followed by stirring at room temperature for 90 minutes. The residue obtained by distilling off the
20 solvent under reduced pressure was recrystallized from a mixed solvent of ethanol and diethyl ether, whereby the title compound (0.14 g, 68%) was obtained.

^1H -NMR (DMSO- d_6) δ : 1.30-1.50 (1H, m), 1.90-2.10 (2H, m), 2.40-2.60 (1H, m), 2.60-3.00 (5H, m), 3.03 (4H, m), 3.40-3.80 (4H, br),
25 7.00-7.10 (3H, m), 7.73 (1H, dd, J =8.8, 2.0 Hz),

7.81 (1H, dd, J=8.8, 1.5 Hz), 8.05 (3H, br), 8.18 (1H, d, J=8.3 Hz),
8.20-8.30 (2H, m), 8.49 (1H, s).

MS (FAB) m/z: 498 [(M+H)⁺, Cl³⁵], 500 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₂₈ClN₃O₃S·HCl·3/2H₂O

5 Calculated: C, 55.61; H, 5.74; N, 7.48; Cl, 12.63; S, 5.71.

Found: C, 55.64; H, 5.53; N, 7.77; Cl, 12.79; S, 5.76.

[Example B-2] 1-[[(6RS)-6-Aminomethyl-5,6,7,8-tetrahydronaphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

10 In the same manner as in Example B-1, the title compound was obtained using 1-[[(6RS)-6-(N-tert-butoxycarbonylaminomethyl)-5,6,7,8-tetrahydronaphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

15 ¹H-NMR (DMSO-d₆) δ: 1.30-1.50 (1H, m), 2.00-2.10 (2H, m), 2.40-2.60 (1H, m), 2.60-3.00 (7H, m), 3.00-3.20 (2H, m), 3.30-3.50 (2H, m), 3.82 (2H, m), 4.22 (2H, br), 7.00-7.10 (1H, m), 7.25 (2H, s), 7.73 (1H, dd, J=8.8, 2.4 Hz), 7.81 (1H, dd, J=8.8, 1.5 Hz), 8.00-8.40 (6H, m), 8.52 (1H, s),
20 11.08 (1H, br).

MS (FAB) m/z: 484 [(M+H)⁺, Cl³⁵], 486 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₃₀ClN₃O₂S·2HCl

Calculated: C, 56.07; H, 5.79; N, 7.54; Cl, 19.10; S, 5.76.

Found: C, 56.04; H, 5.79; N, 7.52; Cl, 18.95; S, 5.80.

25 [Example B-3] 1-[[(2RS)-6-Aminomethyl-1,2,3,4-tetrahydronaphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-

yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using 1-[[[(2RS)-6-(N-tert-butoxycarbonylaminomethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine
5 as a starting material.

^1H -NMR (DMSO- d_6) δ : 1.30-1.50(1H,m), 2.00-2.20(1H,m), 2.20-2.40(1H,m), 2.40-2.60(1H,m), 2.75(2H,m), 2.90-3.30(7H,m), 3.60-3.70(2H,m), 3.70-4.00(4H,m), 7.04(1H,d,J=7.8Hz), 7.10-10
7.30(2H,m), 7.74(1H,m), 7.86(1H,d,J=8.8Hz), 8.20-8.50(6H,m), 8.56(1H,s), 10.69(1H,br).

MS (FAB) m/z : 484 $[(M+H)^+, \text{Cl}^{35}]$, 486 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{26}\text{H}_{30}\text{ClN}_3\text{O}_2\text{S} \cdot 2\text{HCl} \cdot 1/2\text{H}_2\text{O}$

Calculated: C, 55.18; H, 5.88; N, 7.42; Cl, 18.79; S, 5.66.

15 Found: C, 55.34; H, 5.70; N, 7.31; Cl, 18.76; S, 5.85.

[Example B-4] 1-[[[(2RS)-6-Aminomethyl-1,2,3,4-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using 1-[[[(2RS)-6-(N-tert-butoxycarbonylaminomethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.
20

^1H -NMR (DMSO- d_6) δ : 1.55(1H,m), 1.80-1.90(1H,m), 2.60-2.90(4H,m), 2.90-3.10(5H,m), 3.50-3.80(4H,m), 3.90(2H,s),
25

7.05 (1H, d, J=7.8 Hz), 7.10-7.20 (2H, m), 7.71 (1H, d, J=8.8 Hz),
7.82 (1H, d, J=8.3 Hz), 8.10-8.40 (6H, m), 8.50 (1H, s).

MS (FAB) m/z: 498 [(M+H)⁺, Cl³⁵], 500 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₂₈ClN₃O₃S·1.2HCl·0.8H₂O

5 Calculated: C, 56.15; H, 5.58; N, 7.55; Cl, 14.02; S, 5.76.

Found: C, 55.93; H, 5.22; N, 7.37; Cl, 14.26; S, 5.70.

[Example B-5] 1-[(7-Aminomethylnaphthalen-2-yl)carbonyl]-
4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine
hydrochloride

10 In the same manner as in Example B-1, the title
compound was obtained using 1-[[7-(N-tert-
butoxycarbonylaminomethyl)naphthalen-2-yl]carbonyl]-4-[(6-
chloronaphthalen-2-yl)sulfonyl]piperazine as a starting
material.

15 ¹H-NMR (DMSO-d₆) δ: 3.10 (4H, br), 3.30-3.90 (4H, br),
4.18 (2H, s), 7.46 (1H, d, J=8.8 Hz), 7.69 (1H, d, J=8.8 Hz),
7.73 (1H, d, J=8.8 Hz), 7.83 (1H, d, J=8.8 Hz), 7.89 (1H, s), 7.90-
8.00 (3H, m), 8.19 (1H, d, J=8.8 Hz), 8.20-8.30 (2H, m), 8.50 (4H, br
s).

20 MS (FAB) m/z: 494 [(M+H)⁺, Cl³⁵], 496 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₂₄ClN₃O₃S·HCl·3/4H₂O

Calculated: C, 57.41; H, 4.91; N, 7.72; Cl, 13.03; S, 5.89.

Found: C, 57.40; H, 4.87; N, 7.71; Cl, 13.09; S, 5.89.

[Example B-6] 1-[(7-Aminomethylnaphthalen-2-yl)methyl]-4-
25 [(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example B-1, the title

compound was obtained using 1-[[7-(N-tert-butoxycarbonylaminomethyl)naphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 2.92 (2H,m), 3.22 (2H,m), 3.83 (2H,m), 4.20 (2H,d,J=5.4Hz), 4.51 (2H,br), 7.60-7.90 (4H,m), 7.90-8.40 (7H,m), 8.52 (1H,s), 8.57 (3H,br), 11.52 (1H,br).
MS (FAB) m/z : 480 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 482 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{26}\text{H}_{26}\text{ClN}_3\text{O}_2\text{S}\cdot 2\text{HCl}\cdot 1/4\text{H}_2\text{O}$

10 Calculated: C, 56.02; H, 5.15; N, 7.54; Cl, 19.08; S, 5.75.
Found: C, 55.88; H, 5.45; N, 7.34; Cl, 18.90; S, 5.69.

[Example B-7] 1-[(6-Aminomethylnaphthalen-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

15 In tetrahydrofuran (5 ml), 2-(N-tert-butoxycarbonylaminomethyl)-6-methoxycarbonylnaphthalene (0.15 g) was dissolved, followed by the addition of 1N sodium hydroxide (0.70 ml). The resulting mixture was stirred at room temperature for 16 hours. After the
20 reaction mixture was concentrated under reduced pressure, the concentrate was diluted with dichloromethane and added with dilute hydrochloric acid to separate the organic layer. The organic layer thus obtained was dried over anhydrous sodium sulfate. The residue obtained by
25 distilling off the solvent under reduced pressure was dissolved in N,N-dimethylformamide (5 ml), followed by the

addition of 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (0.21 g), N-methylmorpholine (54.0 μ l), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (94.0 mg) and 1-hydroxybenzotriazole (77.0 mg). The resulting mixture was stirred at room temperature for 21 hours. The reaction mixture was concentrated under reduced pressure. The concentrate was diluted with ethyl acetate, washed with water and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 100:1), followed by the reaction in the same manner as in Example B-1, whereby the title compound (77.0 g, 29%) was obtained as colorless crystals.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.09(4H,br), 3.40-3.90(4H,br), 4.19(2H,s), 7.47(1H,d,J=8.3Hz), 7.66(1H,d,J=8.3Hz), 7.73(1H,d,J=9.3Hz), 7.83(1H,d,J=8.8Hz), 7.90-8.10(4H,m), 8.19(1H,d,J=8.8Hz), 8.20-8.30(2H,m), 8.40-8.60(4H,m).
MS (FAB) m/z: 494 [(M+H) $^+$, Cl 35], 496 [(M+H) $^+$, Cl 37].

Elementary analysis for $\text{C}_{26}\text{H}_{24}\text{ClN}_3\text{O}_3\text{S}\cdot\text{HCl}\cdot\frac{3}{4}\text{H}_2\text{O}\cdot\frac{1}{5}\text{Et}_2\text{O}$

Calculated: C, 57.60; H, 5.14; N, 7.52; Cl, 12.69; S, 5.74.

Found: C, 57.64; H, 5.10; N, 7.12; Cl, 12.69; S, 5.82.

[Example B-8] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(isoquinolin-7-yl)carbonyl]piperazine hydrochloride

In 4N hydrochloric acid, methyl 7-

isoquinolinecarboxylate (J. Org. Chem., 38(21), 3701, 1973) (206 mg) was dissolved, followed by heating under reflux for 4 hours. In the same manner as in Example B-7, a reaction was effected using the residue obtained by distilling off the solvent under reduced pressure and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound (298 mg, 62%) was obtained.

¹H-NMR (DMSO-d₆) δ: 2.95-3.25 (4H, m), 3.40-3.60 (2H, m), 3.70-3.90 (2H, m), 7.73 (1H, dd, J=8.8, 2.0 Hz), 7.84 (1H, d, J=8.8 Hz), 8.05 (1H, d, J=7.3 Hz), 8.20 (1H, d, J=8.8 Hz), 8.25-8.35 (3H, m), 8.41 (1H, d, J=6.4 Hz), 8.45 (1H, s), 8.52 (1H, s), 8.71 (1H, d, J=6.4 Hz), 9.79 (1H, s).

MS (FAB) m/z: 465 [(M+H)⁺, Cl³⁵], 467 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₀ClN₃O₃S·HCl·2.2H₂O

Calculated: C, 53.18; H, 4.72; N, 7.75; Cl, 13.08; S, 5.92.

Found: C, 53.11; H, 4.70; N, 7.60; Cl, 13.01; S, 6.16.

[Example B-9] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(quinolyl-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-7, the title compound was obtained using quinoline-2-carboxylic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials.

¹H-NMR (DMSO-d₆) δ: 3.05 (2H, m), 3.17 (2H, m), 3.62 (2H, m), 3.83 (2H, m), 7.61 (1H, d, J=8.3 Hz), 7.60-7.80 (2H, m), 7.80-

7.90 (2H, m), 7.95 (1H, d, J=8.3 Hz), 8.00 (1H, d, J=7.3 Hz),
8.18 (1H, d, J=8.8 Hz), 8.20-8.40 (2H, m), 8.43 (1H, d, J=8.3 Hz),
8.51 (1H, s).

Elementary analysis for $C_{24}H_{20}ClN_3O_3S$

5 Calculated: C, 61.87; H, 4.33; N, 9.02; Cl, 7.61; S, 6.88.

Found: C, 61.76; H, 4.20; N, 8.73; Cl, 7.65; S, 6.99.

[Example B-10] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
[(4-hydroxyquinolin-2-yl)carbonyl]piperazine hydrochloride

10 In the same manner as in Example B-7, the title
compound was obtained using 4-hydroxyquinoline-2-
carboxylic acid and 1-[(6-chloronaphthalen-2-
yl)sulfonyl]piperazine hydrochloride as starting materials.

1H -NMR (DMSO- d_6) δ : 3.00-3.30 (4H, br), 3.53 (2H, br),
3.77 (2H, br), 6.45 (1H, s), 7.48 (1H, t, J=7.3 Hz), 7.70-
15 7.90 (4H, m), 8.10-8.40 (4H, m), 8.52 (1H, s).

MS (FAB) m/z : 482 $[(M+H)^+, Cl^{35}]$, 484 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{24}H_{20}ClN_3O_4S \cdot 9/10HCl \cdot 1/3CH_3OH$,
3/2H₂O

Calculated: C, 52.90; H, 4.60; N, 7.61; Cl, 12.19; S, 5.80.

20 Found: C, 53.17; H, 4.59; N, 7.39; Cl, 12.31; S, 6.07.

[Example B-11] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
[(8-hydroxyquinolin-7-yl)carbonyl]piperazine hydrochloride

25 In the same manner as in Example B-7, the title
compound was obtained using 8-hydroxyquinoline-7-
carboxylic acid and 1-[(6-chloronaphthalen-2-
yl)sulfonyl]piperazine hydrochloride as starting materials.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.90-3.30 (4H, br), 3.35 (2H, br),
 3.79 (2H, br), 7.39 (1H, d, $J=8.3\text{Hz}$), 7.53 (1H, d, $J=8.3\text{Hz}$), 7.60-
 7.90 (3H, m), 8.10-8.40 (3H, m), 8.50 (1H, s),
 8.60 (1H, d, $J=7.8\text{Hz}$), 8.96 (1H, d, $J=4.4\text{Hz}$).

5 MS (FAB) m/z : 482 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 484 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{24}\text{H}_{20}\text{ClN}_3\text{O}_4\text{S}\cdot\text{HCl}\cdot\text{CH}_3\text{OH}\cdot 1/4\text{H}_2\text{O}$

Calculated: C, 54.11; H, 4.63; N, 7.57; Cl, 12.78; S, 5.78.

Found: C, 54.40; H, 4.84; N, 7.66; Cl, 13.04; S, 5.99.

10 [Example B-12] 1-[(Benzimidazol-5-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example B-7, the title compound was obtained using methyl N-triphenylmethyl-5-benzimidazolecarboxylate and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials.

15 $^1\text{H-NMR}$ (DMSO-d_6) δ : 3.08 (4H, br), 3.30-4.00 (4H, br),
 7.48 (1H, d, $J=8.3\text{Hz}$), 7.60-7.90 (4H, m), 8.10-8.30 (3H, m),
 8.50 (1H, s), 9.51 (1H, s).

MS (FAB) m/z : 455 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 457 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{22}\text{H}_{19}\text{ClN}_4\text{O}_3\text{S}\cdot\text{HCl}\cdot 5/4\text{H}_2\text{O}$

20 Calculated: C, 51.42; H, 4.41; N, 10.90; Cl, 13.80; S, 6.24.

Found: C, 51.53; H, 4.40; N, 10.71; Cl, 13.61; S, 6.40.

25 [Example B-13] 1-[(Benzimidazol-5-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine hydrochloride

In the same manner as in Example B-12, the title compound was obtained using methyl N-triphenylmethyl-5-benzimidazolecarboxylate and 1-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine hydrochloride as starting materials.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.67(1H,m), 1.93(1H,m), 3.20-3.90(8H,m), 7.44(1/2H,m), 7.54(1/2H,m), 7.68(1H,m), 7.80-8.00(3H,m), 8.10-8.30(3H,m), 8.49(1/2H,s), 8.55(1/2H,s), 9.56 and 9.57(1H,each s).

MS (FAB) m/z : 469 $[(M+H)^+, \text{Cl}^{35}]$, 471 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{23}\text{H}_{21}\text{ClN}_4\text{O}_3\text{S}\cdot\text{HCl}\cdot 0.3\text{CH}_3\text{OH}\cdot\text{H}_2\text{O}$

Calculated: C, 52.50; H, 4.76; N, 10.51; Cl, 13.30; S, 6.01.

Found: C, 52.31; H, 4.66; N, 10.50; Cl, 13.34; S,

6.01.

[Example B-14] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(thiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-7, the title compound was obtained using sodium thiazolo[5,4-c]pyridine-2-carboxylate and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 3.10-3.30(4H,m), 3.84(2H,m),

4.32(2H,m), 7.69(1H,dd, $J=8.8, 2.0\text{Hz}$),

7.83(1H,dd, $J=8.8, 2.0\text{Hz}$), 8.10-8.30(4H,m), 8.51(1H,s),

8.79(1H,d,J=5.9Hz), 9.62(1H,s).

MS (FAB) m/z: 473 [(M+H)⁺, Cl³⁵], 475 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₁H₁₇ClN₄O₃S₂·HCl

Calculated: C, 49.51; H, 3.56; N, 11.00; Cl, 13.92; S,

5 12.59.

Found: C, 49.45; H, 3.71; N, 11.20; Cl, 13.67; S,

12.55.

[Example B-15] 1-[(E)-4-Chlorostyrylsulfonyl]-4-

[(thiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

10 hydrochloride

In the same manner as in Example B-7, the title compound was obtained using sodium thiazolo[5,4-c]pyridine-2-carboxylate and 1-[(E)-4-chlorostyrylsulfonyl]piperazine hydrochloride as starting materials.

15 ¹H-NMR (DMSO-d₆) δ: 3.30(4H,m), 3.87(2H,m), 4.35(2H,m),

7.35(1H,d,J=15.6Hz), 7.40-7.50(3H,m), 7.79(1H,d,J=8.3Hz),

8.22(1H,d,J=5.9Hz), 8.77(1H,d,J=5.9Hz), 9.59(1H,s).

MS (FAB) m/z: 449 [(M+H)⁺, Cl³⁵], 451 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₁₉H₁₇ClN₄O₃S₂·1/2HCl

20 Calculated: C, 48.85; H, 3.78; N, 11.99; Cl, 11.38; S,

13.73.

Found: C, 49.18; H, 3.80; N, 12.20; Cl, 11.05; S,

13.84.

[Example B-16] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-

25 [(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-

yl)methyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using 1-[(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.82-2.88 (4H,m), 2.91-2.99 (4H,m), 3.28-3.36 (2H,m), 3.47-3.55 (4H,m), 4.02 (2H,br s), 6.58 (1H,s), 7.71 (1H,dd, $J=8.8, 2.0\text{Hz}$), 7.81 (1H,dd, $J=8.8, 2.0\text{Hz}$), 7.23-7.28 (3H,m), 8.49 (1H,s), 9.42 (2H,br s).

MS (FAB) m/z : 462 $[(M+H)^+, \text{Cl}^{35}]$, 464 $[(M+H)^+, \text{Cl}^{37}]$.

[Example B-17] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[trans-3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propenoyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using 1-[trans-3-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propenoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.95-3.10 (6H,m), 3.32-3.51 (3H,m), 3.60-3.80 (3H,m), 4.12 (2H,s), 6.75 (1H,d, $J=15.1\text{Hz}$), 7.19 (1H,s), 7.50 (1H,d, $J=15.1\text{Hz}$), 7.70 (1H,dd, $J=8.8, 2.4\text{Hz}$), 7.81 (1H,dd, $J=8.8, 2.0\text{Hz}$), 8.15 (1H,d, $J=8.8\text{Hz}$), 8.22 (1H,d, $J=2.0\text{Hz}$), 8.50 (1H,s), 9.53 (2H,br s).

MS (FAB) m/z : 502 $[(M+H)^+, \text{Cl}^{35}]$, 504 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{24}\text{H}_{24}\text{ClN}_3\text{O}_3\text{S}_2 \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$

Calculated: C, 52.65; H, 4.79; Cl, 12.95; N, 7.67; S, 11.71.

Found: C, 52.36; H, 4.88; Cl, 12.63; N, 8.01; S, 11.39.

5 [Example B-18] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propionyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using 1-[3-(5-tert-butoxycarbonyl-
10 4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propionyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

¹H-NMR (DMSO-d₆) δ: 2.80-3.60 (16H,m), 4.12 (2H,br s),
7.11 (1H,br s), 7.74 (1H,dd,J=8.8,2.0Hz),
15 7.83 (1H,dd,J=8.8,2.0Hz), 8.20 (1H,s), 8.25-8.30 (2H,m),
8.53 (1H,s), 9.67 (2H,br s).

MS (FAB) m/z: 504 [(M+H)⁺, Cl³⁵], 506 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₆ClN₃O₃S₂·1.2HCl·1.3H₂O

Calculated: C, 50.46; H, 5.26; Cl, 13.65; N, 7.36.

20 Found: C, 50.83; H, 5.26; Cl, 13.43; N, 6.97.

[Example B-19] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propyl]piperazine hydrochloride

In the same manner as in Example B-1, the title
25 compound was obtained using 1-[3-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propyl]-4-[(6-

chloronaphthalen-2-yl)sulfonyl]piperazine
as a starting material.

¹H-NMR (DMSO-d₆) δ: 1.90-2.07 (2H,m), 2.72-2.80 (2H,m), 2.82-
3.21 (8H,m), 3.35 (2H,br s), 3.51 (2H,d,J=11.5Hz),
5 3.82 (2H,d,J=11.5Hz), 4.06 (2H,s), 6.66 (1H,s),
7.74 (1H,dd,J=8.8,1.5Hz), 7.85 (1H,dd,J=8.8,1.5Hz),
8.20 (1H,d,J=8.8Hz), 8.25-8.39 (2H,m), 8.55 (1H,s), 9.50 (2H,br
s), 11.26 (1H,br s).

MS (FAB) m/z: 490 [(M+H)⁺, Cl³⁵], 492 [(M+H)⁺, Cl³⁷].

10 Elementary analysis for C₂₄H₂₈ClN₃O₂S₂·2HCl·1.6H₂O
Calculated: C, 48.71; H, 5.65; Cl, 17.97; N, 7.10; S,
10.84.

Found: C, 49.01; H, 5.77; Cl, 17.62; N, 6.96; S,
10.82.

15 [Example B-20] 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[N-
[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-
yl)methyl]carbamoyl]piperazine hydrochloride

In the same manner as in Example B-1, the title
compound was obtained using 1-[N-[(5-tert-butoxycarbonyl-
20 4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-
yl)methyl]carbamoyl]-4-[(6-chloronaphthalen-2-
yl)sulfonyl]piperazine as a starting material.

¹H-NMR (DMSO-d₆) δ: 2.78-2.86 (2H,br s), 2.88-2.94 (4H,m),
3.29-3.35 (2H,m), 3.37-3.42 (4H,m), 4.03 (2H,br s),
25 4.19 (2H,d,J=5.4Hz), 6.62 (1H,s), 7.25 (1H,t,J=5.4Hz),

7.72 (1H, dd, J=8.8, 2.0Hz), 7.82 (1H, dd, J=8.8, 2.0Hz),
8.16 (1H, d, J=8.8Hz), 8.22-8.26 (2H, m), 8.50 (1H, s), 9.27 (2H, br
s).

Elementary analysis for $C_{23}H_{25}ClN_4O_3S_2 \cdot HCl \cdot 1.3H_2O$

5 Calculated: C, 48.90; H, 5.10; Cl, 12.55; N, 9.92.

Found: C, 49.02; H, 5.20; Cl, 12.50; N, 9.76.

[Example B-21] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-
yl)carbonyl]piperazine hydrochloride

10 In the same manner as in Example B-1, the title
compound was obtained using 1-[(5-tert-butoxycarbonyl-
4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-4-
[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting
material.

15 1H -NMR (DMSO- d_6) δ : 2.99-3.05 (2H, m), 3.08 (4H, t, J=4.6Hz),
3.35-3.40 (2H, m), 3.71 (4H, t, J=4.6Hz), 4.11 (2H, s),
7.17 (1H, s), 7.71 (1H, dd, J=8.8, 2.0Hz),
7.82 (1H, dd, J=8.8, 2.0Hz), 8.22-8.28 (3H, m), 8.50 (1H, s),
9.38 (2H, br s).

20 MS (FAB) m/z: 476 $[(M+H)^+, Cl^{35}]$, 478 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{22}H_{23}ClN_3O_3S_2 \cdot HCl \cdot 3/2H_2O$

Calculated: C, 48.98; H, 4.86; Cl, 13.14; N, 7.79; S,
11.89.

Found: C, 48.96; H, 4.67; Cl, 13.21; N, 7.74; S,

25 11.93.

[Example B-22] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-

ethoxycarbonyl-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using 1-[(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine as a starting material.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.22 (3H, t, $J=7.0\text{Hz}$), 2.38-2.58 (1H, m), 2.65-2.72 (1H, m), 3.04 (2H, br s), 3.29-3.43 (3H, m), 3.70 (1H, br s), 4.01-4.30 (6H, m), 5.18 (1H, br s), 7.27 (1H, s), 7.73 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.82 (1H, d, $J=8.8\text{Hz}$), 8.26 (1H, s), 8.29 (1H, s), 8.54 (1H, s), 9.59 (2H, br s).

MS (FAB) m/z : 548 $[(M+H)^+, \text{Cl}^{35}]$, 550 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{25}\text{H}_{26}\text{N}_3\text{ClO}_5\text{S}_2 \cdot 1.2\text{HCl} \cdot 0.6\text{H}_2\text{O}$

Calculated: C, 49.83; H, 4.75; Cl, 12.94; N, 6.97; S, 10.64.

Found: C, 49.62; H, 4.71; Cl, 13.30; N, 7.19; S, 10.56.

[Example B-23] 2-Carboxy-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In tetrahydrofuran (1 ml), 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (95 mg) was dissolved, followed by the addition of ethanol (2 ml) and 1N sodium hydroxide (3 ml).

The resulting mixture was heated under reflux for 30 minutes. To the reaction mixture, 4N hydrochloric acid (2 ml) was added and the precipitate thus obtained was collected by filtration, whereby the title compound (83 mg, 90%) was obtained as a colorless foam.

¹H-NMR (DMSO-d₆) δ: 2.30-2.53 (1H,m), 2.58-2.69 (1H,m), 3.04 (2H,br s), 3.29-3.83 (4H,m), 4.07-4.32 (4H,m), 4.90-5.20 (1H,m), 7.03-7.30 (1H,m), 7.71 (1H,dd,J=8.8,2.4Hz), 7.81 (1H,d,J=8.8Hz), 8.81 (1H,d,J=8.8Hz), 8.20-8.29 (2H,m), 8.52 (1H,s), 9.58 (2H,br s).

MS (FAB) m/z: 520 [(M+H)⁺, Cl³⁵], 522 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₃H₂₂N₃ClO₅S₂·1.2HCl·0.8H₂O

Calculated: C, 47.78; H, 4.32; Cl, 13.49; N, 7.27; S, 11.09.

Found: C, 47.41; H, 4.36; Cl, 13.81; N, 7.14; S, 11.01.

[Example B-24] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-aminohydroxyiminomethyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine

To methanol (4 ml), a solution of 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(5-cyano-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine (41 mg) in dichloromethane (1 ml) was added, followed by the addition of hydroxylamine hydrochloride (28 mg) and triethylamine (0.55 ml). The resulting mixture was stirred at room temperature for 2 hours. The residue obtained by

concentrating the reaction mixture under reduced pressure was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 100:3), whereby the title compound (14 mg, 32%) was obtained.

5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 2.74-2.79(2H,m), 3.06(4H,s), 3.35-3.38(2H,m), 3.71(4H,s), 4.07(2H,s), 5.32(2H,s), 7.08(1H,s), 7.71(1H,dd,J=8.8,1.6Hz), 7.81(1H,dd,J=8.8,1.6Hz), 8.16(1H,s), 8.23-8.25(2H,m), 8.33(1H,br s), 8.49(1H,s).
MS (FAB) m/z : 534 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 536 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

10 [Example B-25] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[N-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbamoyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using 1-[N-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbamoyl]-4-
15 [(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.83(2H,br s), 2.99(4H,br s), 3.30(2H,br s), 3.54(4H,br s), 4.00(2H,s), 6.33(1H,s),
20 7.70(1H,dd,J=8.8,2.0Hz), 7.82(1H,d,J=8.8Hz), 8.16(1H,d,J=8.8Hz), 8.22(1H,s), 8.26(1H,d,J=8.8Hz), 8.50(1H,s), 9.18(2H,br s), 9.82(1H,s).
MS (FAB) m/z : 491 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 493 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{22}\text{H}_{23}\text{N}_4\text{ClO}_3\text{S}_2 \cdot \text{HCl} \cdot 0.3\text{H}_2\text{O}$
25 Calculated: C, 49.59; H, 4.65; Cl, 13.31; N, 10.51; S,

12.03.

Found: C, 49.32; H, 4.63; Cl, 13.34; N, 10.81; S,

12.03.

[Example B-26] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[N-methyl-N-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbamoyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using 1-[N-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)-N-methylcarbamoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

¹H-NMR (DMSO-d₆) δ: 2.83(2H,d,J=5.4Hz), 2.97(4H,br s), 3.10(3H,s), 3.28-3.41(6H,m), 4.00(2H,s), 6.35(1H,s), 7.72(1H,dd,J=8.8,2.0Hz), 7.81(1H,dd,J=8.8,2.0Hz), 8.17(1H,d,J=8.8Hz), 8.23-8.31(2H,m), 8.50(1H,s), 9.28(2H,br s).

MS (FAB) m/z: 505 [(M+H)⁺, Cl³⁵], 507 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₃H₂₅N₄ClO₃S₂·1.1HCl·0.5H₂O

Calculated: C, 49.85; H, 4.93; Cl, 13.43; N, 10.11; S,

11.57.

Found: C, 49.55; H, 4.92; Cl, 13.23; N, 10.13; S,

11.83.

[Example B-27] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(1-pyrrolin-2-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl]carbonyl]piperazine hydrochloride

In N,N-dimethylformamide (20 ml), 1-[(6-

chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (400 mg) was dissolved, followed by the addition of triethylamine (0.16 ml) and 2-methoxypyrroline (464 mg). The resulting mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure. To the residue, 1N hydrochloric acid was added and the precipitate thus formed was collected by filtration, whereby the title compound (411 mg, 88%) was obtained as a pale yellow foamy solid.

¹H-NMR (DMSO-d₆) δ: 2.07-2.18 (2H,m), 2.90-3.11 (8H,m), 3.62 (2H,t,J=6.8Hz), 3.72 (4H,br), 3.80 (2H,t,J=5.9Hz), 3.99 (2H,t,J=5.9Hz), 4.62 (1H,br s), 4.73 (1H,br s), 7.10 (1H,s), 7.50 (1H,s), 7.72 (1H,dd,J=8.8,2.0Hz), 7.82 (1H,dd,J=8.8,2.0Hz), 8.18 (1H,d,J=8.8Hz), 8.22-8.28 (2H,m), 8.51 (1H,s), 10.37 (1H,br s), 10.53 (1H,br s).

MS (FAB) m/z: 542 [(M+H)⁺, Cl³⁵], 544 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₂₇ClN₄O₃S₂·1.3HCl·0.4H₂O

Calculated: C, 52.25; H, 4.91; Cl, 13.64; N, 9.37; S, 10.73.

Found: C, 52.34; H, 5.03; Cl, 13.56; N, 9.36; S, 10.74.

[Example B-28] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-1, the title

compound was obtained using 1-[(6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

¹H-NMR (DMSO-d₆) δ: 3.01(2H,t,J=5.9Hz), 3.11(4H,br), 3.44(2H,br s), 3.74(2H,br s), 4.32-4.46(4H,m), 7.71(1H,dd,J=8.8,2.0Hz), 7.83(1H,dd,J=8.8,2.0Hz), 8.15(1H,d,J=8.8Hz), 8.23(1H,s), 8.26(1H,d,J=8.8Hz), 8.30(1H,s).

MS (FAB) m/z: 477 [(M+H)⁺, Cl³⁵], 479 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₁H₂₁ClN₄O₃S₂·HCl·0.2H₂O

Calculated: C, 48.78; H, 4.37; Cl, 13.71; N, 10.84; S, 12.40.

Found: C, 48.60; H, 4.50; Cl, 13.58; N, 10.62; S,

12.29.

[Example B-29] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-aminohydroxyiminomethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride; and 1-[(6-carbamoyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In a similar manner to Referential Example 33 and Example B-24 by using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride as a starting material, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(6-

aminohydroxyiminomethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride and also
 1-[(6-carbamoyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine were obtained.

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-aminohydroxyiminomethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride:

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.77(2H, br s), 3.09(4H, br),
 3.48(2H, t, $J=5.4\text{Hz}$), 3.73(2H, br s), 4.30-4.50(4H, m),
 5.61(1H, br s), 7.71(1H, dd, $J=8.8\text{Hz}, 2.0\text{Hz}$),
 7.82(1H, dd, $J=8.8, 2.0\text{Hz}$), 8.15(1H, d, $J=8.8\text{Hz}$),
 8.22(1H, d, $J=1.5\text{Hz}$), 8.25(1H, d, $J=8.8\text{Hz}$), 8.50(1H, s),
 8.53(1H, br s).

MS (FAB) m/z : 535 $[(M+H)^+, \text{Cl}^{35}]$, 537 $[(M+H)^+, \text{Cl}^{37}]$.

1-[(6-Carbamoyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine:

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.75(2H, br s), 3.09(4H, br),
 3.63(2H, t, $J=5.9\text{Hz}$), 3.73(2H, br s), 4.39(2H, br s),
 4.59(2H, s), 6.17(2H, s), 7.70(1H, dd, $J=8.8, 2.0\text{Hz}$),
 7.82(1H, dd, $J=8.8, 2.0\text{Hz}$), 8.14(1H, d, $J=8.8\text{Hz}$),
 8.21(1H, d, $J=1.5\text{Hz}$), 8.25(1H, d, $J=8.8\text{Hz}$), 8.50(1H, s).

MS (FAB) m/z : 520 $[(M+H)^+, \text{Cl}^{35}]$, 522 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{22}\text{H}_{22}\text{ClN}_5\text{O}_4\text{S}_2 \cdot \text{H}_2\text{O}$

Calculated: C, 49.11; H, 4.50; N, 13.02.

Found: C, 48.98; H, 4.12; N, 12.83.

[Example B-30] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
[[6-(1-pyrrolin-2-yl)-4,5,6,7-tetrahydrothiazolo[5,4-
c]pyridin-2-yl]carbonyl]piperazine hydrochloride

In the same manner as in Example B-27, the title
compound was obtained using 1-[(6-chloronaphthalen-2-
yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-
2-yl)carbonyl]piperazine hydrochloride as a starting
material.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.07-2.15 (2H,m), 2.94-3.16 (8H,m),
3.63 (2H,t,J=7.3Hz), 3.75 (2H,br s), 3.90 (2H,br s),
4.39 (2H,br s), 4.93 (2H,s), 7.70 (1H,dd,J=8.8,2.0Hz),
7.83 (1H,dd,J=8.8,2.0Hz), 8.15 (1H,d,J=8.8Hz),
8.22 (1H,d,J=2.0Hz), 8.25 (1H,d,J=8.8Hz), 8.50 (1H,s).

MS (FAB) m/z : 544 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 546 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{25}\text{H}_{26}\text{ClN}_5\text{O}_3\text{S}_2 \cdot 1.4\text{HCl} \cdot \text{CH}_3\text{OH}$

Calculated: C, 49.79; H, 5.05; Cl, 13.57; N, 11.17; S,
10.23.

Found: C, 49.44; H, 4.78; Cl, 13.63; N, 10.83; S,
10.15.

[Example B-31] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
[(6-formyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazine

In the same manner as in Example B-7, the title
compound was obtained using 1-[(6-chloronaphthalen-2-

yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride and formic acid as starting materials.

¹H-NMR (DMSO-d₆) δ: 2.74-2.88 (2H,m), 3.10 (4H,br),
 5 3.31 (2H,s), 3.66-3.86 (4H,m), 4.64-4.73 (2H,m),
 7.69 (1H,dd,J=8.8,2.0Hz), 7.82 (1H,dd,J=8.8,2.0Hz),
 8.14 (1H,d,J=8.8Hz), 8.15-8.22 (2H,m), 8.24 (1H,d,J=8.8Hz),
 8.50 (1H,s).

MS (FAB) m/z: 505 [(M+H)⁺, Cl³⁵], 507 [(M+H)⁺, Cl³⁷].

10 Elementary analysis for C₂₂H₂₁ClN₄O₄S₂·1/5H₂O

Calculated: C, 51.95; H, 4.24; Cl, 6.97; N, 11.02; S,
 12.61.

Found: C, 52.18; H, 4.30; Cl, 6.69; N, 10.71; S,
 12.21.

15 [Example B-32] 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-
 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In dichloromethane (10 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (400 mg) was
 20 suspended, followed by the addition of triethylamine (0.22 ml) and acetic acid (0.05 ml). The resulting mixture was stirred at room temperature for 5 minutes. To the reaction mixture, a 30% aqueous solution (0.08 ml) of formaldehyde
 25 and sodium triacetoxyborohydride (264 mg) were added. The resulting mixture was stirred at room temperature for 10

minutes. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue. The resulting mixture was washed with water and saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in a saturated hydrochloride solution in ethanol (1 ml), followed by concentration under reduced pressure. The residue thus obtained was crystallized from hexane and ethyl acetate, whereby the title compound (298 mg, 71%) was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.89(3H,s), 3.10(6H,br), 3.32-3.81(4H,m), 4.30-4.81(4H,m), 7.71(1H,dd, $J=8.8, 2.0\text{Hz}$), 7.82(1H,dd, $J=8.8, 2.0\text{Hz}$), 8.15(1H,d, $J=8.8\text{Hz}$), 8.20-8.28(2H,m), 8.50(1H,s), 11.28(1H,br s).

MS (FAB) m/z : 491 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 493 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{22}\text{H}_{23}\text{ClN}_4\text{O}_3\text{S}_2 \cdot \text{HCl} \cdot 0.6\text{H}_2\text{O}$

Calculated: C, 49.09; H, 4.72; Cl, 13.17; N, 10.41; S, 11.91.

Found: C, 48.88; H, 4.78; Cl, 13.26; N, 10.42; S, 12.03.

[Example B-33] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6,6-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridinium iodide

In N,N-dimethylformamide (20 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

hydrochloride (200 mg) was dissolved, followed by the addition of methyl iodide (0.05 ml) and potassium carbonate (79.0 mg). The resulting mixture was stirred overnight at 80°C. The reaction mixture was concentrated under reduced pressure. Water was added to the residue and the precipitate so formed was collected by filtration. The precipitate was dissolved in a 1:1 mixed solution of dichloromethane and methanol. Ethyl acetate was added to the resulting solution and the precipitate thus formed was collected by filtration, whereby the title compound (144 mg, 56%) was obtained.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 3.05-3.23 (12H, m), 3.77 (2H, t, $J=5.9\text{Hz}$), 4.40 (2H, br s), 4.79 (2H, br s), 7.71 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.83 (1H, dd, $J=8.8, 2.0\text{Hz}$), 8.15 (1H, d, $J=8.8\text{Hz}$), 8.20-8.27 (2H, m), 8.52 (1H, s).

MS (FD) m/z : 505 (M^+ , Cl^{35}), 507 (M^+ , Cl^{37}).

Elementary analysis for $\text{C}_{23}\text{H}_{26}\text{ClIN}_4\text{O}_3\text{S}_2 \cdot 1/2\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$

Calculated: C, 44.35; H, 4.47; N, 8.28.

Found: C, 44.52; H, 4.23; N, 8.01.

[Example B-34] 2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine N-oxide

In acetone (10 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (400 mg) was suspended, followed by the addition of a 1N aqueous

solution (0.38 ml) of sodium hydroxide and a 30% aqueous solution (3.50 ml) of hydrogen peroxide. The resulting mixture was stirred at room temperature for 8 days. After the reaction mixture was concentrated under reduced pressure, the residue was purified by chromatography through a synthetic adsorbent ("Diaion® HP-20", trade name; water ~ water : acetonitrile = 2:5), whereby the title compound (84 mg, 39%) was obtained.

¹H-NMR (DMSO-d₆) δ: 2.83-2.90 (1H,m), 3.10 (5H,br), 3.20-3.47 (4H,m), 3.61-3.83 (3H,m), 4.28-4.50 (3H,m), 4.78-4.85 (1H,m), 7.69 (1H,dd,J=8.8,2.0Hz), 7.82 (1H,dd,J=8.8,2.0Hz), 8.14 (1H,d,J=8.8Hz), 8.19-8.27 (2H,m), 8.50 (1H,s).

MS (FD) m/z: 506 (M⁺, Cl³⁵), 508 (M⁺, Cl³⁷).

[Example B-35] 2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine trifluoroacetate

To trifluoroacetic acid (1 ml), a solution of 1-[(6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine (303 mg) dissolved in dichloromethane (1 ml) was added, followed by concentration under reduced pressure. The precipitate thus formed was collected by filtration and washed with diethyl ether, whereby the title compound (263 mg, 83%) was obtained.

¹H-NMR (DMSO-d₆) δ: 2.39-2.70 (2H,m), 2.92-3.06 (2H,m), 3.42-3.77 (4H,m), 4.25-4.50 (7/2H,m), 4.97 (1/2H,br s), 5.35-5.44 (1/2H,m), 6.14 (1/2H,br s), 7.30-7.39 (1H,m), 7.66-7.73 (2H,m), 7.77-7.82 (1H,m), 8.16 (1H,d,J=8.8Hz), 8.21-8.28 (2H,m), 8.49 (1H,s), 9.26 (2H,br s).

MS (FAB) m/z: 520 [(M+H)⁺, Cl³⁵], 522 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₂₂ClN₅O₄S₂·CF₃CO₂H·0.6H₂O

Calculated: C, 44.29; H, 3.73; Cl, 5.40; F, 9.55; N, 10.67; S, 9.77.

Found: C, 44.59; H, 3.79; Cl, 5.26; F, 9.54; N, 10.28; S, 9.72.

[Example B-36] 2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-32, the title compound was obtained using 2-carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine trifluoroacetate as a starting material.

¹H-NMR (DMSO-d₆) δ: 2.37-2.70 (2H,m), 2.91 (3H,s), 3.00-3.78 (6H,m), 4.28-4.77 (7/2H,m), 4.97 (1/2H,br s), 5.40-5.50 (1/2H,m), 6.14 (1/2H,br s), 7.32-7.40 (1H,m), 7.68-7.75 (2H,m), 7.77-7.83 (1H,m), 8.15 (1H,d,J=8.8Hz), 8.21-8.28 (2H,m), 8.49 (1H,s).

MS (FAB) m/z: 534 [(M+H)⁺, Cl³⁵], 536 [(M+H)⁺, Cl³⁷].

Elementary analysis for $C_{23}H_{24}ClN_5O_4S_2 \cdot HCl \cdot 2.5H_2O$

Calculated: C, 44.88; H, 4.91; Cl, 11.52; N, 11.38; S, 10.42.

Found: C, 44.83; H, 4.89; Cl, 11.65; N, 11.31; S, 10.46.

[Example B-37] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(2-hydroxyethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine hydrochloride

The crude product, which had been obtained by the reaction in the same manner as in Example B-32 by using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (132 mg) and glyoxylic hydrate (82 mg) as starting materials, was suspended in tetrahydrofuran (50 ml). Triethylamine (0.22 ml) and ethyl chloroformate (0.03 ml) were added to the resulting suspension under ice cooling, followed by stirring at room temperature for 15 minutes. To the reaction mixture, sodium borohydride (50 mg) and water (10 ml) were added to the reaction mixture and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane, washed with saturated aqueous NaCl solution and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica

gel column (dichloromethane ~ dichloromethane : methanol = 100:3), followed by dissolution in saturated hydrochloride in ethanol (1 ml). The resulting solution was then concentrated under reduced pressure. The concentrate was pulverized and washed in ethyl acetate, whereby the title compound (52 mg, 33%) was obtained.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 3.11(4H, br s), 3.20-3.57(6H, m), 3.69-3.87(4H, m), 4.34-4.82(4H, m), 5.38(1H, br s), 7.71(1H, dd, $J=8.8, 2.0\text{Hz}$), 7.82(1H, dd, $J=8.8, 2.0\text{Hz}$), 8.15(1H, d, $J=8.8\text{Hz}$), 8.22(1H, s), 8.25(1H, d, $J=8.8\text{Hz}$), 8.50(1H, s), 10.48(1H, br s).

MS (FAB) m/z : 521 $[(M+H)^+, \text{Cl}^{35}]$, 523 $[(M+H)^+, \text{Cl}^{37}]$.

In the same manner as in Example B-32, the compounds of Examples B-38, B-39 and B-40 were obtained, respectively by using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride as a starting material.

[Example B-38] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(pyridin-2-yl)methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine hydrochloride

$^1\text{H-NMR}$ (DMSO- d_6) δ : 3.07-3.17(6H, m), 3.63(2H, t, $J=6.3\text{Hz}$), 3.74(2H, br s), 4.39(2H, br s), 4.58(2H, s), 4.61(2H, s), 7.50-7.64(1H, m), 7.67-7.73(2H, m), 7.82(1H, dd, $J=8.8, 1.5\text{Hz}$), 7.97(1H, m), 8.15(1H, d, $J=8.8\text{Hz}$), 8.22(1H, d, $J=1.5\text{Hz}$), 8.25(1H, d, $J=8.8\text{Hz}$), 8.50(1H, s), 8.69(1H, d, $J=4.9\text{Hz}$).

MS (FAB) m/z : 568 $[(M+H)^+, Cl^{35}]$, 570 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{27}H_{26}ClN_5O_3S_2 \cdot 2HCl \cdot 0.8H_2O$

Calculated: C, 49.48; H, 4.55; Cl, 16.23; N, 10.68; S, 9.78.

5 Found: C, 49.72; H, 4.48; Cl, 16.31; N, 10.86; S, 9.53.

[Example B-39] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
[[6-(pyridin-3-yl)methyl-4,5,6,7-tetrahydrothiazolo[5,4-
c]pyridin-2-yl]carbonyl]piperazine hydrochloride

10 1H -NMR (DMSO- d_6) δ : 3.03-3.27(6H,m), 3.40-3.81(4H,m),
3.74(2H,br s), 4.40(2H,br s), 4.50(2H,s), 4.70(2H,s),
7.70(1H,dd,J=8.8,2.4Hz), 7.82(1H,d,J=8.8Hz),
8.15(1H,d,J=8.8Hz), 8.22(1H,s), 8.25(1H,d,J=8.8Hz),
8.50(1H,s), 8.73(1H,d,J=7.8Hz), 8.93(1H,d,J=4.4Hz).

15 MS (FAB) m/z : 568 $[(M+H)^+, Cl^{35}]$, 570 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{27}H_{26}ClN_5O_3S_2 \cdot 2.9HCl \cdot 4.5H_2O$

Calculated: C, 42.96; H, 5.06; Cl, 18.32; N, 9.28.

Found: C, 42.97; H, 4.84; Cl, 18.19; N, 9.23.

[Example B-40] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
20 [[6-(pyridin-4-yl)methyl-4,5,6,7-tetrahydrothiazolo[5,4-
c]pyridin-2-yl]carbonyl]piperazine hydrochloride

1H -NMR (DMSO- d_6) δ : 3.11(4H,br s), 3.19(2H,br s),
3.64(2H,br s), 3.74(2H,br s), 4.41(2H,br s), 4.49(2H,s),
4.80(2H,s), 7.69(1H,dd,J=8.8,2.0Hz),

25 7.82(1H,dd,J=8.8,2.0Hz), 8.15(1H,d,J=8.8Hz),

8.21 (1H, d, J=2.0Hz), 8.25 (1H, d, J=8.8Hz), 8.41 (2H, d, J=6.3Hz),
8.50 (1H, s), 9.04 (2H, d, J=6.3Hz).

MS (FAB) m/z: 568 [(M+H)⁺, Cl³⁵], 570 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₇H₂₆ClN₅O₃S₂·2.7HCl·6.0H₂O

5 Calculated: C, 41.86; H, 5.30; Cl, 16.93; N, 9.04; S, 8.28.

Found: C, 42.05; H, 4.98; Cl, 16.92; N, 9.37; S, 8.61.

[Example B-41] 1-[(E)-4-Chlorostyrylsulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

10 In the same manner as in Example B-1, the title compound was obtained using 1-[(6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(E)-4-chlorostyrylsulfonyl]piperazine as a starting material.

15 ¹H-NMR (DMSO-d₆) δ: 3.04 (2H, br s), 3.23 (4H, br), 3.47 (2H, br s), 3.77 (2H, br s), 4.35-4.50 (2H, m), 7.33 (1H, d, J=15.6Hz), 7.43 (1H, d, J=15.6Hz), 7.49 (1H, d, J=8.3Hz), 7.79 (1H, d, J=8.3Hz), 9.57 (2H, br s).

MS (FAB) m/z: 453 [(M+H)⁺, Cl³⁵], 455 [(M+H)⁺, Cl³⁷].

20 Elementary analysis for C₁₉H₂₁ClN₄O₃S₂·HCl·0.3H₂O

Calculated: C, 46.12; H, 4.60; Cl, 14.33; N, 11.32; S, 12.96.

Found: C, 46.42; H, 4.66; Cl, 14.38; N, 11.02; S, 13.02.

25 [Example B-42] 1-[(E)-4-Chlorostyrylsulfonyl]-4-[6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-32, the title compound was obtained using 1-[(E)-4-chlorostyrylsulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride as a starting material.

¹H-NMR (DMSO-d₆) δ: 2.92(3H,s), 3.01-3.32(6H,br), 3.35-3.88(4H,m), 4.29-4.84(4H,m), 7.33(1H,d,J=15.6Hz), 7.49(1H,d,J=15.6Hz), 7.49(1H,d,J=8.3Hz), 7.79(1H,d,J=8.3Hz), 11.31(1H,br s).

MS (FAB) m/z: 467 [(M+H)⁺, Cl³⁵], 469 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₀H₂₃ClN₄O₃S₂·HCl·0.2H₂O

Calculated: C, 47.37; H, 4.85; Cl, 13.98; N, 11.05; S, 12.65.

Found: C, 47.30; H, 4.92; Cl, 14.05; N, 11.03; S, 12.49.

[Example B-43] (3S)-3-[(6-Chloronaphthalen-2-yl)sulfonamido]-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]pyrrolidine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using (3S)-1-[(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]-3-[(6-chloronaphthalen-2-yl)sulfonamido]pyrrolidine as a starting material.

[α]_D = -69.72° (25°C, c=1.00, CH₃OH).

¹H-NMR (DMSO-d₆ at 100°C) δ: 1.88-1.89(1H,m), 2.10-
 2.25(1H,m), 3.02-3.07(2H,m), 3.10-3.50(6H,m), 4.02(1H,s),
 4.12(2H,s), 4.45(2H,s), 7.12(1H,s), 7.65(1H,d,J=8.3Hz),
 7.91(1H,d,J=8.3Hz), 8.10(1H,d,J=8.3Hz), 8.14(1H,s),
 5 8.16(1H,d,J=8.3Hz), 8.18(1H,br s), 8.48(1H,s), 9.65(2H,br
 s).

MS (FD) m/z: 461 (M⁺, Cl³⁵), 463 (M⁺, Cl³⁷).

Elementary analysis for C₂₂H₂₄ClN₃O₂S₂·2.1HCl·H₂O

Calculated: C, 47.47; H, 5.09; Cl, 19.74; N, 7.55; S,
 10 11.52.

Found: C, 47.55; H, 5.13; Cl, 19.85; N, 7.45; S,
 11.48.

[Example B-44] (3S)-3-[(6-Chloronaphthalen-2-
 yl)sulfonamido]-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-
 15 2-yl)carbonyl]pyrrolidine hydrochloride

In the same manner as in Example B-1, the title
 compound was obtained using (3S)-1-[(5-tert-butoxycarbonyl-
 4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-3-
 [(6-chloronaphthalen-2-yl)sulfonamido]pyrrolidine as a
 20 starting material.

[α]_D²⁰ = -62.70° (25°C, c=1.00, CH₃OH).

¹H-NMR (DMSO-d₆ at 100°C) δ: 1.82-1.90(1H,m), 1.96-
 2.05(1H,m), 3.05(2H,t,J=6.0Hz), 3.42-3.57(2H,m), 3.60-
 3.72(2H,m), 3.84-3.90(1H,m), 4.12(2H,s), 4.45(2H,s),
 25 7.25(1H,s), 7.64(1H,dd,J=8.3,1.6Hz),

7.90 (1H, dd, J=8.3, 1.6Hz), 7.97 (1H, d, J=5.6Hz),
 8.08 (1H, d, J=8.7Hz), 8.12 (1H, s), 8.14 (1H, d, J=8.7Hz),
 8.47 (1H, s), 9.55 (2H, br s).

MS (FAB) m/z: 476 [(M+H)⁺, Cl³⁵], 478 [(M+H)⁺, Cl³⁷].

5 Elementary analysis for C₂₂H₂₂ClN₃O₃S₂.HCl

Calculated: C, 51.56; H, 4.52; Cl, 13.84; N, 8.20; S,
 12.51.

Found: C, 51.25; H, 4.61; Cl, 13.68; N, 7.98; S,
 12.36.

10 [Example B-45] (3S)-1-[(6-Chloronaphthalen-2-yl)sulfonyl]-
 3-[[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-
 yl)methyl]amino]pyrrolidine hydrochloride

In the same manner as in Example B-1, the title
 compound was obtained using (3S)-3-[[(5-tert-
 15 butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-
 yl)methyl]amino]-1-[(6-chloronaphthalen-2-
 yl)sulfonyl]pyrrolidine as a starting material.

[α]_D=+34.82° (25°C, c=1.00, CH₃OH).

¹H-NMR (DMSO-d₆) δ: 1.98-2.20 (2H, m), 2.99-3.04 (2H, m), 3.19-
 20 3.26 (1H, m), 3.30-3.50 (3H, m), 3.61-3.72 (1H, m), 3.52-
 3.60 (1H, m), 4.13 (2H, s), 4.29 (2H, s), 7.09 (1H, s),
 7.71 (1H, dd, J=8.8, 2.0Hz), 7.89 (1H, dd, J=8.8, 2.0Hz),
 8.17 (1H, d, J=8.8Hz), 8.25 (1H, d, J=2.0Hz), 8.30 (1H, s),
 8.57 (1H, s), 9.55 (2H, br s), 9.7-10.0 (1H, m).

25 MS (FD) m/z: 461 (M⁺, Cl³⁵), 463 (M⁺, Cl³⁷).

Elementary analysis for $C_{22}H_{24}ClN_3O_2S_2 \cdot 2HCl \cdot 0.2H_2O$

Calculated: C, 49.06; H, 4.94; Cl, 19.75; N, 7.80; S, 11.91.

Found: C, 48.88; H, 4.97; Cl, 19.65; N, 7.67; S, 11.84.

[Example B-46] (3S)-3-[(4,5,6,7-Tetrahydrothieno[3,2-c]pyridin-2-yl)carbonylamino]-1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using (3S)-3-[(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonylamino]-1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine as a starting material.

$[\alpha]_D^{25} = +33.56^\circ$ (25°C, $c=1.00$, CH_3OH).

1H -NMR ($DMSO-d_6$) δ : 1.85-1.95 (1H,m), 1.95-2.05 (1H,m), 3.04 (2H,m), 3.24-3.40 (1H,m), 3.41-3.53 (3H,m), 4.04-4.24 (3H,m), 7.34 (1H,s), 7.67 (1H,d, $J=8.8$ Hz), 7.84 (1H,d, $J=8.8$ Hz), 8.03 (1H,d, $J=8.8$ Hz), 8.17 (1H,s), 8.22 (1H,d, $J=8.8$ Hz), 8.27 (1H,d, $J=5.7$ Hz), 8.50 (1H,s), 9.59 (1H,br s), 9.71 (1H,br s).

MS (FD) m/z : 476 $[(M+H)^+, Cl^{35}]$, 478 $[(M+H)^+, Cl^{37}]$.

[Example B-47] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]homopiperazine hydrochloride

In the same manner as in Example B-1, the title

compound was obtained using 1-[(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine as a starting material.

5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.83(2H, br s), 3.04(2H, t, $J=5.4\text{Hz}$), 3.30-3.59(6H, m), 3.60-3.88(4H, m), 4.14(2H, s), 7.20(1H, br s), 7.69(1H, dd, $J=8.8, 2.0\text{Hz}$), 7.84(1H, d, $J=8.8\text{Hz}$), 8.10(1H, d, $J=8.8\text{Hz}$), 8.17-8.21(2H, m), 8.50(1H, s), 9.57(2H, br s).

10 MS (FAB) m/z : 490 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 492 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{23}\text{H}_{25}\text{ClN}_3\text{O}_3\text{S}_2 \cdot 1.1\text{HCl} \cdot 0.2\text{H}_2\text{O}$

Calculated: C, 51.66; H, 4.99; Cl, 13.92; N, 7.86.

Found: C, 51.46; H, 4.61; Cl, 13.55; N, 8.05.

[Example B-48] 4-[(6-Chloronaphthalen-2-yl)sulfonamido]-1-
15 [(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperidine hydrochloride

In the same manner as in Examples B-7 and B-1, the title compound was obtained using 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-carboxylic acid
20 (WO94/21599) and 4-[(6-chloronaphthalen-2-yl)sulfonamido]piperidine trifluoroacetate as starting materials.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.26-1.38(2H, m), 1.58-1.65(2H, m), 2.93-3.13(4H, m), 3.29-3.40(3H, m), 3.90-4.05(2H, m), 4.11(2H, s),
25 7.16(1H, s), 7.68(1H, dd, $J=8.0, 2.0\text{Hz}$),

7.92 (1H, dd, J=8.8, 2.0 Hz), 8.07 (1H, d, J=7.3 Hz),
 8.13 (2H, d, J=8.8 Hz), 8.20 (1H, d, J=7.3 Hz), 8.23 (1H, s),
 8.51 (1H, s), 9.71 (2H, br s).

MS (FAB) m/z: 490 [(M+H)⁺, Cl³⁵], 492 [(M+H)⁺, Cl³⁷].

5 Elementary analysis for C₂₃H₂₅ClN₃O₃S₂·2.4HCl·3H₂O

Calculated: C, 43.67; H, 5.32; Cl, 19.05; N, 6.64.

Found: C, 43.85; H, 5.10; Cl, 19.07; N, 6.63.

[Example B-49] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-

[(6-aminohydroxyiminomethylbenzofuran-2-

10 yl)carbonyl]piperazine

In the same manner as in Example B-24, the title compound was obtained using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(6-cyanobenzofuran-2-yl)carbonyl]piperazine as a starting material.

15 ¹H-NMR (DMSO-d₆) δ: 3.11 (4H, s), 3.83 (4H, br), 5.90 (2H, br s),

7.34 (1H, s), 7.64-7.75 (3H, m), 7.83 (1H, dd, J=8.8, 2.0 Hz),

7.89 (1H, s), 8.17 (1H, d, J=8.8 Hz), 8.23 (1H, d, J=1.5 Hz),

8.26 (1H, d, J=8.8 Hz), 8.51 (1H, s), 9.77 (1H, s).

MS (FAB) m/z: 513 [(M+H)⁺, Cl³⁵], 515 [(M+H)⁺, Cl³⁷].

20 Elementary analysis for C₂₄H₂₁ClN₄O₅S·1/5H₂O

Calculated: C, 55.80; H, 4.18; Cl, 6.86; N, 10.70; S, 6.21.

Found: C, 55.65; H, 4.25; Cl, 6.81; N, 10.70; S, 6.37.

[Example B-50] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-

[(5-aminohydroxyiminomethylbenzothiophen-2-

25 yl)carbonyl]piperazine

In the same manner as in Example B-24, the title

compound was obtained using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(5-cyanobenzothiophen-2-yl)carbonyl]piperazine as a starting material.

¹H-NMR (DMSO-d₆) δ: 3.11(4H,s), 3.77(4H,s), 5.87(2H,br s),
 5 7.67(1H,s), 7.71(1H,d,J=2.0Hz), 7.75(1H,d,J=8.8Hz),
 7.83(1H,dd,J=8.8,2.0Hz), 7.94(1H,d,J=8.8Hz), 8.15(1H,s),
 8.17(1H,d,J=8.8Hz), 8.25(1H,d,J=8.8Hz), 8.29(1H,d,J=8.3Hz),
 8.50(1H,s), 9.68(1H,s).

MS (FAB) m/z: 529 [(M+H)⁺, Cl³⁵], 531 [(M+H)⁺, Cl³⁷].

10 Elementary analysis for C₂₄H₂₁N₄ClO₄S₂·0.3H₂O

Calculated: C, 53.94; H, 4.07; N, 10.48.

Found: C, 54.22; H, 4.17; N, 10.23.

[Example B-51] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
 [(1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]piperazine
 15 hydrochloride

In the same manner as in Example B-1, the title
 compound was obtained using 1-[(2-tert-butoxycarbonyl-
 1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]-4-[(6-
 chloronaphthalen-2-yl)sulfonyl]piperazine as a starting
 20 material.

¹H-NMR (DMSO-d₆) δ: 2.89-3.29(4H,m), 3.20-3.83(8H,m),
 4.25(2H,s), 7.10-7.25(3H,m), 7.71(1H,d,J=8.3Hz),
 7.81(1H,d,J=8.3Hz), 8.17(1H,d,J=8.8Hz), 8.15-8.25(2H,m),
 8.49(1H,s), 9.54(2H,br s).

25 MS (FAB) m/z: 470 [(M+H)⁺, Cl³⁵], 472 [(M+H)⁺, Cl³⁷].

Elementary analysis for $C_{24}H_{24}ClN_3O_3S \cdot HCl \cdot 2.0H_2O$

Calculated: C, 53.14; H, 5.39; Cl, 13.07; N, 7.75; S, 5.91.

Found: C, 53.43; H, 5.43; Cl, 13.15; N, 8.07; S, 5.55.

[Example B-52] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-
 5 [(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-
 yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-32, the title
 compound was obtained using 1-[(6-chloronaphthalen-2-
 yl)sulfonyl]-4-[(1,2,3,4-tetrahydroisoquinolin-6-
 10 yl)carbonyl]piperazine hydrochloride as a starting
 material.

1H -NMR (DMSO- d_6) δ : 2.88 (3H, s), 2.90-3.80 (13H, m), 4.12-
 4.56 (1H, m), 7.19 (1H, s), 7.20 (2H, d, $J=6.8$ Hz),
 7.72 (1H, dd, $J=8.8, 2.0$ Hz), 7.81 (1H, d, $J=8.8$ Hz),
 15 8.17 (1H, d, $J=8.8$ Hz), 8.24-8.28 (2H, m), 8.49 (1H, s),
 10.93 (1H, br s).

MS (FAB) m/z : 484 $[(M+H)^+, Cl^{35}]$, 486 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{24}H_{24}ClN_3O_3S \cdot HCl \cdot 2.3H_2O$

Calculated: C, 53.44; H, 5.67; Cl, 12.62; N, 7.48; S, 5.71.

20 Found: C, 53.71; H, 5.81; Cl, 12.37; N, 7.26; S, 5.62.

[Example B-53] 6-[[4-[(6-Chloronaphthalen-2-
 yl)sulfonyl]piperazin-1-yl]carbonyl]-2,2-dimethyl-1,2,3,4-
 tetrahydroisoquinolinium iodide

In the same manner as in Example B-33, the title
 25 compound was obtained using 1-[(6-chloronaphthalen-2-
 yl)sulfonyl]-4-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-

yl)carbonyl]piperazine hydrochloride as a starting material.

¹H-NMR (DMSO-d₆) δ: 2.90-3.85 (18H, m), 4.61 (2H, s),
7.19 (1H, d, J=7.8 Hz), 7.24 (1H, d, J=7.8 Hz), 7.28 (1H, s),
5 7.72 (1H, dd, J=8.8, 1.5 Hz), 7.81 (1H, d, J=8.8 Hz),
8.17 (1H, d, J=8.8 Hz), 8.20-8.31 (2H, m), 8.50 (1H, s).

Elementary analysis for C₂₆H₂₉ClIN₃O₃S·H₂O

Calculated: C, 48.49; H, 4.85; N, 6.53.

Found: C, 48.66; H, 4.96; N, 6.39.

10 [Example B-54] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

A reaction was effected in the same manner as in Example B-7 by using 1-[(5-chloroindol-2-yl)sulfonyl]piperazine and lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-carboxylate as starting
15 materials, whereby the title compound was obtained as brown amorphous.

¹H-NMR (CDCl₃) δ: 2.49 (3H, s), 2.78-2.83 (2H, m), 2.85-
20 2.94 (2H, m), 3.15-3.28 (4H, br), 3.67 (2H, s), 3.82-3.95 (2H, br),
4.50-4.65 (2H, br), 6.96 (1H, d, J=2.0 Hz),
7.32 (1H, dd, J=8.8, 2.0 Hz), 7.36 (1H, d, J=8.8 Hz), 7.67 (1H, s),
8.71 (1H, br).

MS (FAB) m/z: 480 [(M+H)⁺, Cl³⁵], 482 [(M+H)⁺, Cl³⁷].

25 Elementary analysis for C₂₀H₂₂ClN₅O₃S₂·HCl·0.5H₂O

Calculated: C, 44.64; H, 4.76; Cl, 13.18; N, 13.02; S, 11.92.

Found: C, 44.69; H, 4.72; Cl, 13.36; N, 12.76; S, 11.76.

5 In a similar manner to Example B-54, the compounds shown in Examples B-55 to B-60 were synthesized.

[Example B-55] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
10 hydrochloride

¹H-NMR (DMSO-d₆) δ: 2.50-2.63 (3H,m), 2.65-2.74 (2H,m), 2.92 (3H,s), 3.00-3.14 (2H,m), 3.22-3.42 (2H,m), 3.63-3.78 (2H,m), 4.23-4.29 (1H,m), 4.35-4.47 (1H,m), 4.64-4.80 (1H,m), 4.97-5.02 (1/2H,m), 5.45-5.51 (1H,m), 6.13-
15 6.17 (1/2H,m), 7.02 (1H,br), 7.32 (1H,dd,J=8.8,2.0Hz), 7.47 (1H,d,J=8.3Hz), 7.77 (1H,br), 8.07-8.16 (1H,m), 12.41 (1H,s).

MS (FAB) m/z: 537 [(M+H)⁺, Cl³⁵], 539 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₂₅ClN₆O₄S₂·HCl·1.7H₂O

20 Calculated: C, 43.74; H, 4.90; Cl, 11.74; N, 13.91; S, 10.62.

Found: C, 44.02; H, 5.07; Cl, 11.83; N, 13.59; S, 10.52.

[Example B-56] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)carbonyl]piperazine hydrochloride
25

¹H-NMR (DMSO-d₆) δ: 2.65 (3H, d, J=4.5Hz), 2.85-3.22 (7H, m),
 3.22-3.38 (2H, m), 3.66 (1H, d, J=12.2Hz), 3.55-3.68 (2H, m),
 4.17-4.40 (3H, m), 4.55-4.68 (1H, m), 6.99 (1H, d, J=2.0Hz), 7.27-
 7.31 (2H, m), 7.48 (1H, d, J=8.8Hz), 7.77 (1H, d, J=2.0Hz),
 8.09 (1H, br s), 10.60 (1H, br s), 12.41 (1H, s).

MS (FAB) m/z: 536 [(M+H)⁺, Cl³⁵], 538 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₃H₂₆ClN₅O₄S₂·1.3HCl·0.6H₂O·1.5EtOH

Calculated: C, 47.07; H, 5.70; Cl, 12.29; N, 10.56; S,
 9.67.

Found: C, 46.68; H, 5.63; Cl, 12.16; N, 10.20; S,
 10.06.

[Example B-57] 1-[(5-Chlorobenzo[b]furan-2-yl)sulfonyl]-4-
 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 yl)carbonyl]piperazine

¹H-NMR (DMSO-d₆) δ: 2.91 (3H, s), 3.11 (2H, br), 3.25-
 3.90 (4H, m), 3.76 (2H, br), 5.35-4.80 (2H, br), 4.41 (2H, br),
 7.46 (1H, d, J=8.8Hz), 7.73 (1H, s), 7.84 (1H, d, J=8.8Hz),
 7.96 (1H, s), 11.48 (1H, br).

MS (FAB) m/z: 481 [(M+H)⁺, Cl³⁵], 483 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₀H₂₁ClN₄O₄S₂·1.1HCl·0.3H₂O

Calculated: C, 45.63; H, 4.35; Cl, 14.14; N, 10.64; S,
 12.18.

Found: C, 45.81; H, 4.29; Cl, 13.93; N, 10.44; S,
 12.26.

[Example B-58] 1-[(6-Chlorobenzo[b]furan-2-yl)sulfonyl]-4-

[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

¹H-NMR (DMSO-d₆) δ: 2.91(3H,s), 3.00-3.55(7H,m), 3.60-3.85(3H,m), 4.42(3H,br), 4.67(1H,br), 7.46(1H,d,J=8.8Hz),
 5 7.73(1H,s), 7.84(1H,d,J=8.8Hz), 7.96(1H,s), 11.48(1H,br).

MS (FAB) m/z: 481 [(M+H)⁺, Cl³⁵], 483 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₀H₂₁ClN₄O₄S₂·HCl·0.17H₂O

Calculated: C, 46.15; H, 4.33; Cl, 13.62; N, 10.76; S, 12.32.

10 Found: C, 46.45; H, 4.41; Cl, 13.61; N, 10.58; S, 12.02.

[Example B-59] 1-[(5-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

15 ¹H-NMR (DMSO-d₆) δ: 2.91(3H,s), 2.98-3.90(10H,m), 4.24-4.77(4H,m), 7.60(1H,d,J=8.8Hz), 8.05(1H,s), 8.10-8.21(2H,m), 11.72(1H,br s).

MS (FAB) m/z: 497 [(M+H)⁺, Cl³⁵], 499 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₀H₂₁ClN₄O₃S₃·HCl·0.9H₂O

20 Calculated: C, 43.70; H, 4.36; Cl, 12.90; N, 10.19; S, 17.50.

Found: C, 43.82; H, 4.49; Cl, 13.27; N, 9.86; S, 17.32.

[Example B-60] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

25

yl)carbonyl]piperazine hydrochloride

¹H-NMR (DMSO-d₆) δ: 2.91(3H,s), 3.02-3.25(5H,m), 3.32-3.90(6H,m), 4.33-4.55(2H,m), 4.64-4.75(1H,m), 7.55(1H,dd,J=8.8,2.0Hz), 8.06(1H,d,J=8.8Hz), 8.09(1H,s), 11.42(1H,br s).

MS (FAB) m/z: 497 [(M+H)⁺, Cl³⁵], 499 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₀H₂₁ClN₄O₃S₃·1.1HCl·1.4H₂O

Calculated: C, 42.71; H, 4.46; Cl, 13.24; N, 9.96; S, 17.11.

Found: C, 42.49; H, 4.51; Cl, 13.01; N, 9.76; S, 16.95.

[Example B-61] 2-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(thiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine was treated and purified in the same manner as in Example B-33, whereby the title compound was obtained.

IR(KBr)cm⁻¹: 3016, 1631, 1450, 1432, 1344, 1328, 1276, 1267, 1162, 1135, 998, 727, 578.

¹H-NMR (DMSO-d₆) δ: 3.10-3.23(4H,m), 3.85(2H,br s), 4.29(2H,br s), 4.48(3H,s), 7.70(1H,dd,J=8.8,2.0Hz), 7.83(1H,d,J=8.8,2.0Hz), 8.17(1H,d,J=8.8Hz), 8.23(1H,d,J=2.0Hz), 8.26(1H,d,J=8.8Hz), 8.52(1H,s), 8.71(1H,d,J=6.8Hz), 8.98(1H,d,J=6.8,2.0Hz),

9.92 (1H, d, J=2.0Hz) .

MS (FAB) m/z: 487 [M⁺, Cl³⁵], 489 [M⁺, Cl³⁷].

[Example B-62] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-
[(N-methyl)carbamoyl]-1-[(6-methyl-4,5,6,7-

5 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
hydrochloride

In N,N-dimethylformamide (100 ml), lithium 6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-carboxylate (616
mg), 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-[(N-
10 methyl)carbamoyl]piperazine trifluoroacetate (1.12 g), 1-
hydroxybenzotriazole monohydrate (36 mg) and 1-
(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
(579 mg) were dissolved and the resulting solution was
stirred overnight at room temperature. The reaction
15 mixture was concentrated under reduced pressure.
Dichloromethane was then added to the residue, followed by
washing with water. The organic layer was dried over
anhydrous sodium sulfate and distilled under reduced
pressure to remove the solvent. The residue was purified
20 by chromatography on a silica gel column [Φ 3.0 x (1.5 +
8) cm, ethyl acetate : methanol = 100:4], whereby a
colorless foam was obtained. The resulting foam was
dissolved in 1N HCl (20 ml), followed by concentration
under reduced pressure, whereby the title compound (845 mg)
25 was obtained as a pale yellow foam.

IR(KBr)cm⁻¹: 3380, 1668, 1623, 1542, 1415, 1342, 1330,

1159, 1135, 1078, 952, 941, 723, 578.

¹H-NMR (DMSO-d₆) δ: 2.42-2.80 (5H,m), 2.90 (3H,s), 2.95-
3.80 (6H,m), 4.23-4.50 (5/2H,m), 4.60-4.77 (1H,m),
4.98 (1/2H,br s), 5.45-5.55 (1H,m), 6.15 (1/2H,br s),
5 7.71 (1H,d,J=8.8Hz), 7.78-7.82 (1H,m), 8.07-8.13 (1H,m),
8.15 (1H,d,J=8.8Hz), 8.23 (1H,s), 8.25 (1H,d,J=8.8Hz),
8.49 (1H,s), 11.70-12.00 (1H,m).

MS (FAB) m/z: 548 [(M+H)⁺, Cl³⁵], 550 [(M+H)⁺, Cl³⁷].

10 In a similar manner to Example B-62, the compounds of
Examples B-63 to B-76 were obtained.

[Example B-63] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-
[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]-2-[[(morpholin-4-yl)carbonyl]methyl]piperazine
hydrochloride

15 Starting materials: lithium 6-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-
chloronaphthalen-2-yl)sulfonyl]-3-[[(morpholin-4-
yl)carbonyl]methyl]piperazine hydrochloride

¹H-NMR (DMSO-d₆) δ: 2.35-2.83 (2H,m), 2.89 (3H,s), 2.95-
20 3.88 (18H,m), 4.31-4.45 (3/2H,m), 4.67 (2H,d,J=15.1Hz),
5.03 (0.5H,br s), 5.37 (0.5H,d,J=13.7Hz), 5.79 (1/2H,br s),
7.70 (1H,dd,J=8.8,2.0Hz), 7.81 (1H,d,J=8.8Hz),
8.15 (1H,d,J=8.8Hz), 8.23 (1H,s), 8.27 (1H,d,J=8.8Hz),
8.50 (1H,s), 11.50-11.75 (1H,m).

25 MS (FAB) m/z: 618 [(M+H)⁺, Cl³⁵], 620 [(M+H)⁺, Cl³⁷].

Elementary analysis for $C_{28}H_{32}ClN_5O_5S_2 \cdot 1.5HCl \cdot 3H_2O$

Calculated: C, 46.27; H, 5.48; Cl, 12.19; N, 9.63; S, 8.82.

Found: C, 46.49; H, 5.20; Cl, 12.16; N, 9.67; S, 8.88.

[Example B-64] N-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]-
 5 1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 yl)carbonyl]piperazin-2-yl]carbonyl]glycine ethyl ester

Starting materials: lithium 6-methyl-4,5,6,7-
 tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, N-[[1-[(6-
 chloronaphthalen-2-yl)sulfonyl]piperazin-3-
 10 yl]carbonyl]glycine ethyl ester trifluoroacetate

1H -NMR (DMSO- d_6) δ : 1.17-1.24 (3H,m), 2.38 (3H,s), 2.39-
 2.53 (1H,m), 2.58-2.84 (5H,m), 3.20-3.29 (1H,m), 3.54-
 3.81 (4H,m), 3.90-4.00 (1H,m), 4.06-4.17 (1H,m),
 4.32 (1H,d,J=11.7Hz), 4.47 (1/2H,d,J=13.7Hz), 5.14 (1/2H,s),
 15 5.66 (1/2H,d,J=13.7Hz), 6.42 (1H,br s), 7.68 (1H,d,J=8.3Hz),
 7.79 (1H,d,J=8.3Hz), 8.12 (1H,dd,J=8.8,3.4Hz), 8.19 (1H,s),
 8.23 (1H,d,J=8.8Hz), 8.48 (1H,s), 8.52 (1/2H,t,J=5.4Hz),
 8.61 (1/2H,t,J=5.4Hz).

MS (FD) m/z: 619 [M^+ , Cl^{35}], 621 [M^+ , Cl^{37}].

20 Elementary analysis for $C_{27}H_{30}ClN_5O_6S_2 \cdot 0.2HCl \cdot 0.1H_2O$

Calculated: C, 51.54; H, 4.87; Cl, 6.76; N, 11.13; S,
 10.19.

Found: C, 51.31; H, 4.92; Cl, 6.74; N, 10.92; S,
 10.01.

25 In the present reaction, the below-described compound
 whose ester bond had been hydrolyzed was obtained.

N-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]carbonyl]glycine

¹H-NMR (DMSO-d₆) δ: 2.37(3H,s), 2.59-2.83(6H,m), 3.20-

5 3.32(1H,m), 3.52-3.77(4H,m), 3.82-3.95(1H,m), 4.28-

4.35(1H,m), 4.45(1/2H,d,J=13.7Hz), 5.13(1/2H,br s),

5.63(1/2H,d,J=13.7Hz), 6.36(1H,br s), 7.69(1H,d,J=8.3Hz),

7.80(1H,d,J=8.3Hz), 8.12(1H,dd,J=8.8,3.4Hz), 8.20(1H,s),

8.23(1H,d,J=8.8Hz), 8.41(1/2H,t,J=5.4Hz), 8.45-

10 8.50(3/2H,m).

MS (FD) m/z: 592 [(M+H)⁺, Cl³⁵], 594 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₇H₃₀ClN₅O₆S₂·H₂O

Calculated: C, 49.22; H, 4.63; Cl, 5.81; N, 11.48; S, 10.51.

15 Found: C, 49.11; H, 4.78; Cl, 6.02; N, 11.41; S, 10.25.

[Example B-65] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-

[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-(morpholin-4-yl)carbamoyl]piperazine

20 hydrochloride

Starting materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[N-(morpholin-4-yl)carbamoyl]piperazine trifluoroacetate

25 ¹H-NMR (DMSO-d₆ at 100°C) δ: 2.58-2.84(8H,m), 2.89(3H,s),

2.98-3.58 (3H,m), 3.40-3.80 (8H,m), 4.10-4.70 (4H,m),
 7.65 (1H,dd,J=8.6,2.4Hz), 7.79 (1H,dd,J=8.6,1.2Hz),
 8.09 (1H,d,J=8.6Hz), 8.14 (1H,s), 8.18 (1H,d,J=8.6Hz),
 8.42 (1H,s), 8.58 (1H,br s).

5 MS (FAB) m/z: 619 [(M+H)⁺, Cl³⁵], 621 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₆ClN₄O₅S₂·1.7HCl·1.7H₂O

Calculated: C, 45.56; H, 5.11; Cl, 13.45; N, 10.57; S,
 8.93.

Found: C, 45.35; H, 5.34; Cl, 13.46; N, 12.01; S,

10 8.93.

[Example B-66] Ethyl N'-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl)carbonyl]hydrazinoacetate

15 hydrochloride

Starting materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, ethyl N'-[[1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-3-yl)carbonyl]hydrazinoacetate hydrochloride

20 ¹H-NMR (DMSO-d₆) δ: 1.18-1.28 (3H,m), 2.36 (3H,s), 2.65-2.85 (5H,m), 3.23-3.28 (1H,m), 3.31 (2H,s), 3.44-3.75 (4H,m), 4.08-4.24 (3H,m), 4.38 (1/2H,d,J=13.7Hz), 5.01 (1/2H,s), 5.22-5.31 (1H,m), 5.52 (1/2H,d,J=13.7Hz), 6.10 (1/2H,br s), 7.69 (1H,d,J=8.8,2.0Hz), 7.72-7.80 (1H,m), 7.72-7.80 (3H,m),
 25 8.47 (1H,s), 9.77-9.85 (1H,m).

MS (FAB) m/z: 635 [(M+H)⁺, Cl³⁵], 637 [(M+H)⁺, Cl³⁷].

Elementary analysis for $C_{27}H_{31}ClN_6O_6S_2 \cdot 1.6HCl \cdot H_2O$

Calculated: C, 45.58; H, 4.90; Cl, 12.95; N, 11.81; S, 9.01.

Found: C, 45.71; H, 5.09; Cl, 12.83; N, 11.46; S, 8.94.

[Example B-67] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(morpholin-4-yl)carbonyl]methyl]carbamoyl]piperazine hydrochloride

Starting materials : lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[N-[(morpholin-4-yl)carbonyl]methyl]carbamoyl]piperazine hydrochloride

1H -NMR (DMSO- d_6) δ : 2.35-2.82 (2H,m), 2.90 (3H,s), 2.95-3.30 (2H,m), 3.32-3.86 (13H,m), 4.05-4.20 (1H,m), 4.23-4.50 (2.5H,m), 4.59-4.70 (1H,m), 5.15 (0.5H,s), 5.50 (0.5H,d, $J=12.2$ Hz), 6.30 (0.5H,s), 7.70 (1H,dd, $J=8.8, 2.0$ Hz), 7.80 (1H,d, $J=8.8$ Hz), 8.12-8.38 (4H,m), 8.48 (1H,s), 11.45-11.75 (1H,m).

MS (FAB) m/z : 661 $[(M+H)^+, Cl^{35}]$, 663 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{29}H_{33}ClN_6O_6S_2 \cdot HCl \cdot H_2O$

Calculated: C, 48.67; H, 5.07; Cl, 9.91; N, 11.74; S, 8.96.

Found: C, 48.70; H, 5.03; Cl, 10.23; N, 11.55; S, 9.32.

[Example B-68] 4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

yl)carbonyl]piperazin-2-yl]carbonyl]morpholine
hydrochloride

Starting materials: lithium 6-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 4-[[1-[(6-
5 chloronaphthalen-2-yl)sulfonyl]piperazin-3-
yl]carbonyl]morpholine trifluoroacetate

IR(KBr)cm⁻¹: 3396, 2919, 2854, 1652, 1623, 1457, 1112, 954,
723, 578.

¹H-NMR (DMSO-d₆) δ: 2.62-2.79(1H,m), 2.85-3.92(19H,m),
10 4.02-4.13(1/2H,m), 4.30-4.49(3/2H,m), 4.58-4.80(1H,m),
5.24-5.46(1H,m), 6.28-6.45(1H,m), 7.71(1H,dd,J=8.8,2.0Hz),
7.83(1H,d,J=8.8Hz), 8.12-8.28(3H,m), 8.53(1H,s), 11.30-
11.80(1H,m).

MS (FAB) m/z: 604 [(M+H)⁺, Cl³⁵], 606 [(M+H)⁺, Cl³⁷].

15 [Example B-69] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-
(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

Starting materials: lithium 6-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-
20 chloronaphthalen-2-yl)sulfonyl]-3-
[ethoxycarbonyl]piperazine

¹H-NMR (CDCl₃) δ: 1.25-1.35(3H,m), 2.43-2.94(9H,m),
3.31(1/2H,dt,J=12.7,3.4Hz), 3.60-3.76(2.5H,m),
3.83(1/2H,d,J=11.7Hz), 3.89(1/2H,d,J=11.7Hz), 4.19-
25 4.30(2H,m), 4.42-4.50(1H,m), 4.55(1/2H,14.2Hz),

5.76 (1/2H, 14.2Hz), 7.57 (1H, dd, J=8.3, 1.5Hz),
7.77 (1H, dd, J=8.3, 1.5Hz), 7.89-7.94 (3H, m), 8.34 (1H, s).

MS (FAB) m/z: 563 [(M+H)⁺, Cl³⁵], 565 [(M+H)⁺, Cl³⁷].

[Example B-70] Methyl [4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]acetate

Starting materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-

[methoxycarbonylmethyl]piperazine

IR(KBr)cm⁻¹: 2944, 2846, 2788, 1735, 1619, 1455, 1164.

¹H-NMR (CDCl₃) δ: 2.40-2.92 (10H, m),

3.04 (1H, dd, J=16.1, 8.8Hz), 3.16-3.27 (1/2H, m), 3.42-

3.55 (1/2H, m), 3.60-3.72 (5H, m), 3.83-3.97 (2H, m),

4.60 (1/2H, d, J=13.2Hz), 5.21 (1/2H, br s),

5.70 (1/2H, d, J=13.2Hz), 6.15 (1/2H, br s),

7.57 (1H, dd, J=8.8, 2.0Hz), 7.75 (1H, dd, J=8.8, 2.0Hz), 7.87-

7.95 (3H, m), 8.30 (1H, s).

MS (FAB) m/z: 563 [(M+H)⁺, Cl³⁵], 565 [(M+H)⁺, Cl³⁷].

[Example B-71] 2-[[N-(tert-butoxy)amino]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine trifluoroacetate

Starting materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[(N-tert-

butoxy)carbonyl]piperazine trifluoroacetate

IR(KBr)cm⁻¹: 2979, 1675, 1465, 1199, 1184, 1166, 1135, 721.

¹H-NMR (DMSO-d₆) δ: 1.15-1.25(9H,m), 2.36(3H,s), 2.37-

2.49(1H,m), 2.67-2.84(5H,m), 3.25-3.35(1H,m), 3.59-

5 3.78(3H,m), 4.13-4.25(1H,m), 4.38(1H,d,J=13.2Hz),

5.01(1/2H,br s), 5.52(1/2H,d,J=13.2Hz), 5.14(1/2H,s),

6.21(1/2H,br s), 7.69(1H,dd,J=8.8,2.0Hz), 7.76-7.74(1H,m),

8.14(1H,d,J=8.8Hz), 8.21(1H,s), 8.24(1H,d,J=8.8Hz), 8.47-

8.53(1H,m), 10.75-10.78(1H,m).

10 MS (FAB) m/z: 606 [(M+H)⁺, Cl³⁵], 608 [(M+H)⁺, Cl³⁷].

[Example B-72] [4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-
[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazin-2-yl]acetamide hydrochloride

Starting materials: lithium 6-methyl-4,5,6,7-

15 tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-
chloronaphthalen-2-yl)sulfonyl]-3-

[carbamoylmethyl]piperazine hydrochloride

IR(KBr)cm⁻¹: 1671, 1616, 1465, 1457, 1419, 1332, 1162,
1133, 1124, 1078, 956, 701, 578.

20 ¹H-NMR (DMSO-d₆) δ: 2.30-2.80(4H,m), 2.90(3H,s), 2.93-

3.25(2H,m), 3.30-3.55(1H,m), 3.62-3.88(3H,m), 4.05-

4.43(2.5H,m), 4.60-4.71(1H,m), 5.05(0.5H,br s),

5.34(0.5H,d,J=13.2Hz), 5.69-5.84(0.5H,m), 6.82(0.5H,br s),

6.93(0.5H,br s), 7.37-7.50(1H,m), 7.70(1H,d,J=8.8Hz),

25 7.80(1H,d,J=8.8Hz), 8.10-8.29(3H,m), 8.49(1H,s).

MS (FAB) m/z: 576 [(M+H)⁺, Cl³⁵], 578 [(M+H)⁺, Cl³⁷].

[Example B-73] 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-
[(N-isopropyl)carbamoyl]-1-[(6-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
5 hydrochloride

Starting materials: lithium 6-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-
chloronaphthalen-2-yl)sulfonyl]-3-[(N-
isopropyl)carbamoyl]piperazine hydrochloride

10 IR(KBr)cm⁻¹: 2967, 2933, 1666, 1625, 1542, 1463, 1344,
1332, 1159, 1135, 954, 725, 578.

¹H-NMR (DMSO-d₆) δ: 1.00-1.10(6H,m), 2.50-2.80(2H,m),
2.91(3H,s), 2.93-3.50(4H,m), 3.60-3.79(2H,m), 3.82-
3.95(1H,m), 4.18-4.30(1H,m), 4.32-4.50(1.5H,m), 4.60-
15 4.77(1H,m), 4.97(0.5H,s), 5.03(0.5H,d,J=13.2Hz),
5.90(0.5H,s), 7.70(1H,d,J=8.8Hz), 7.79(1H,d,J=8.8Hz), 7.92-
8.00(1H,m), 8.22(1H,d,J=8.8Hz), 8.18-8.28(2H,m),
8.48(1H,s).

MS (FAB) m/z: 576 [(M+H)⁺, Cl³⁵], 578 [(M+H)⁺, Cl³⁷].

20 [Example B-74] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-
[[piperidin-1-yl)carbonyl]methyl]-1-[(6-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
hydrochloride

Starting materials: lithium 6-methyl-4,5,6,7-
25 tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-
chloronaphthalen-2-yl)sulfonyl]-3-[[piperidin-1-

yl)carbonyl)methyl]piperazine hydrochloride

IR(KBr)cm⁻¹: 2931, 2854, 1623, 1455, 1334, 1159, 1135, 1124, 1078, 954, 700, 578.

¹H-NMR (DMSO-d₆) δ: 1.20-1.70(8H,m), 2.35-2.82(2H,m),
 2.90(3H,s), 2.95-3.88(11H,m), 4.31-4.45(1.5H,m), 4.62-
 4.76(1H,m), 5.03(0.5H,br s), 5.34(0.5H,d,J=13.2Hz),
 5.70(0.5H,br s), 7.70(1H,d,J=8.8Hz), 7.81(1H,d,J=8.8Hz),
 8.15(1H,d,J=8.8Hz), 8.22(1H,s), 8.27(1H,d,J=8.8Hz),
 8.50(1H,s).

MS (FAB) m/z: 616 [(M+H)⁺, Cl³⁵], 618 [(M+H)⁺, Cl³⁷].

[Example B-75] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-
 [[N-(2-methoxybenzyl)]carbamoyl]-1-[(6-methyl-4,5,6,7-
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
 hydrochloride

Starting materials: lithium 6-methyl-4,5,6,7-
 tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-
 chloronaphthalen-2-yl)sulfonyl]-3-[[N-(2-
 methoxybenzyl)]carbamoyl]piperazine hydrochloride

¹H-NMR (DMSO-d₆) δ: 2.42-3.54(9H,m), 3.62-3.85(5H,m), 4.12-
 4.50(3.5H,m), 4.60-4.77(1H,m), 5.09(1/2H,br s), 5.43-
 5.52(1/2H,m), 6.11-6.19(1/2H,m), 6.85-7.00(2H,m), 7.16-
 7.29(2H,m), 7.72(1H,d,J=10.7Hz), 7.80-7.86(1H,m),
 8.16(1H,d,J=8.8Hz), 8.22-8.28(2H,m), 8.50(1H,s), 8.65-
 8.72(1H,m).

MS (FAB) m/z: 654 [(M+H)⁺, Cl³⁵], 656 [(M+H)⁺, Cl³⁷].

[Example B-76] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-
 [[N-(2-methoxyethyl)]carbamoyl]-1-[(6-methyl-4,5,6,7-
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
 hydrochloride

5 Starting materials: lithium 6-methyl-4,5,6,7-
 tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate,
 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-[[N-(2-
 methoxyethyl)]carbamoyl]piperazine
 IR(KBr) cm^{-1} : 2931, 1544, 1463, 1423, 1344, 1332, 1157,
 10 1133, 1078, 954, 943, 723, 578.
 ^1H -NMR (DMSO- d_6) δ : 2.42-2.82 (2H,m), 2.92 (3H,s), 2.95-
 3.79 (13H,m), 4.21-4.80 (3.5H,m), 5.02 (1/2H,br s),
 5.47 (1/2H,d,J=12.2Hz), 6.07 (1/2H,br s),
 7.70 (1H,dd,J=8.8,2.0Hz), 7.79 (1H,d,J=8.8Hz),
 15 8.13 (1H,d,J=8.8Hz), 8.17-8.32 (3H,m), 8.48 (1H,s), 11.09-
 11.40 (1H,m).
 MS (FAB) m/z : 592 [(M+H) $^+$, Cl 35], 594 [(M+H) $^+$, Cl 37].

[Example B-77] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-
 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 20 yl)carbonyl]piperazine-2-carboxylic acid

In tetrahydrofuran (10 ml), 4-[(6-chloronaphthalen-2-
 yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
 (2.08 g) was dissolved, followed by the addition of ethanol
 25 (20 ml) and a 1N aqueous solution (3.70 ml) of sodium
 hydroxide. The resulting mixture was stirred at room

temperature for 1 hour. After concentration of the reaction mixture under reduced pressure, the residue was added with water (20 ml). The precipitate thus formed was collected by filtration, whereby the title compound (1.39 g) was obtained as a pale yellow foam.

IR(KBr)cm⁻¹: 1731, 1625, 1461, 1346, 1332, 1315, 1159, 1135, 1078, 954, 943, 723, 580.

¹H-NMR (DMSO-d₆) δ: 2.32-3.86(11H,m), 4.27(1H,d,J=11.7Hz), 4.35-4.48(3/2H,m), 4.59-4.78(1H,m), 5.21(1/2H,m), 5.38-5.52(1/2H,m), 6.34-6.47(1/2H,m), 7.71(1H,dd,J=8.8,2.0Hz), 7.83(1H,d,J=8.8Hz), 8.16(1H,d,J=8.8Hz), 8.23(1H,s), 8.27(1H,d,J=8.8Hz), 8.53(1H,s), 11.60-11.90(1H,m).

Elementary analysis for C₂₃H₂₃ClN₄O₅S₂·1.3HCl·1.5H₂O

Calculated: C, 45.33; H, 4.51; Cl, 13.38; N, 9.19; S, 10.52.

Found: C, 45.69; H, 4.55; Cl, 13.29; N, 9.21; S, 10.21.

[Example B-78] N'-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]carbonyl]hydrazinoacetic acid

In the same manner as in the Example B-77, the title compound was obtained using ethyl N'-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]carbonyl]hydrazinoacetate hydrochloride as a starting material.

MS (FAB) m/z: 607 [(M+H)⁺, Cl³⁵], 609 [(M+H)⁺, Cl³⁷].

¹H-NMR (DMSO-d₆ at 100°C) δ: 2.41 (3H, s), 2.65-3.30 (6H, m), 3.37-3.77 (8H, m), 4.16 (1H, d, J=12.7 Hz), 7.64 (1H, dd, J=8.7, 2.4 Hz), 7.78 (1H, dd, J=8.7, 1.6 Hz), 8.07 (1H, d, J=8.7 Hz), 8.11 (1H, d, J=1.6 Hz), 8.16 (1H, d, J=8.7 Hz), 8.42 (1H, s).

Elementary analysis for C₂₅H₂₇ClN₆O₆S₂·2H₂O

Calculated: C, 46.69; H, 4.86; N, 13.07; S, 9.97.

Found: C, 46.87; H, 4.86; N, 12.82; S, 9.62.

[Example B-79] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[N-(tetrahydropyran-2-yloxy)]carbamoyl]piperazine

In N,N-dimethylformamide (20 ml), 4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid (141 mg), 2-tetrahydropyranyloxyamine (180 mg), 1-hydroxybenzotriazole monohydrate (11 mg), 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (145 mg) and potassium carbonate (129 mg) were dissolved,

followed by stirring overnight at room temperature. The reaction mixture was concentrated under reduced pressure. Dichloromethane was added to the residue, followed by washing with water. The organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (Φ 0.7 x 25.0 cm, dichloromethane : methanol = 100:3), whereby the title compound (308 mg) was obtained as a colorless foam.

¹H-NMR (CDCl₃) δ : 1.50-1.89(6H,m), 2.45-2.55(3H,m), 2.72-3.00(6H,m), 3.57-3.97(5H,m), 4.28(0.5H,d,J=12.2Hz), 4.35(0.5H,d,J=12.2Hz), 4.52-4.61(0.5H,m), 4.92(0.5H,s), 5.02(0.5H,br s), 5.06-5.10(0.5H,m), 5.55-5.65(0.5H,m), 5.88(0.5H,br s), 6.21(0.5H,br s), 7.51-7.58(1H,m), 7.77-7.93(4H,m), 8.35(1H,s), 9.61(0.5H,br s), 10.10(1H,br s). MS (FAB) m/z: 634 [(M+H)⁺, Cl³⁵], 636 [(M+H)⁺, Cl³⁷].

[Example B-80] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carbohydroxamic acid

In methanol (10 ml), 4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[N-(tetrahydropyran-2-yloxy)]carbamoyl]piperazine (297 mg) was dissolved, followed by the addition of 1N hydrochloric acid (10 ml). The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced

pressure. The residue was purified by "HP-20" (Φ 1.7 x 20.0 cm, acetonitrile : water = 1:5), whereby the title compound (65 mg) was obtained as a pale yellow foam.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.32-2.73(2H,m), 2.91(3H,s), 2.97-
 5 3.30(3H,m), 3.35-3.50(1H,m), 3.63-3.76(2H,m), 4.22-
 4.48(2.5H,m), 4.61-4.75(1H,m), 4.99(0.5H,s),
 5.47(0.5H,d,J=12.2Hz), 6.24(0.5H,s), 7.70(1H,d,J=8.8Hz),
 7.75-7.85(1H,m), 8.15(1H,d,J=8.8Hz), 8.23(1H,s),
 8.25(1H,d,J=8.8Hz), 8.48(1H,s), 10.26(1H,br s), 10.97(1H,br
 10 s).

MS (FAB) m/z : 550 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 552 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Example B-81] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-
 [[N-(2-hydroxybenzyl)]carbamoyl]-1-[(6-methyl-4,5,6,7-
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

15 In dichloromethane (10 ml), 4-[(6-chloronaphthalen-2-
 yl)sulfonyl]-2-[[N-(2-methoxybenzyl)]carbamoyl]-1-[(6-
 methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 yl)carbonyl]piperazine hydrochloride (195 mg) was
 dissolved, followed by the dropwise addition of a boron
 20 tribromide - dichloromethane solution (1.0M, 2.08 ml) at -
 78°C. The reaction mixture was heated to room temperature
 and stirred overnight. To the reaction mixture, methanol
 (2 ml), sodium carbonate (200 mg) and water (3 ml) were
 added to extract the organic layer, followed by drying over
 25 anhydrous sodium sulfate. The solvent was then distilled
 off under reduced pressure. The solid thus precipitated

was collected by filtration while being washed with 1N hydrochloric acid, whereby the title compound (50 mg, 24%) was obtained as a pale yellow solid.

¹H-NMR (DMSO-d₆) δ: 2.36-2.87(9H,m), 3.11-3.28(1H,m), 3.59-
 3.80(3H,m), 4.12-4.45(3.5H,m), 4.48-4.57(1/2H,m),
 5.08(1/2H,br s), 6.19(1/2H,br s), 6.63-6.81(2H,m), 6.98-
 7.15(2H,m), 7.70(1H,dd,J=8.3,1.5Hz), 7.78-7.84(1H,m),
 8.13(1H,d,J=8.8Hz), 8.20-8.28(2H,m), 8.49(1H,s), 8.50-
 8.62(1H,m), 9.45(1/2H,s), 9.50(1/2H,s).

MS (FAB) m/z: 640 [(M+H)⁺, Cl³⁵], 642 [(M+H)⁺, Cl³⁷].

[Example B-82] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridine hydrochloride

To a solution of 6-methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridine (58.1 mg) in tetrahydrofuran (3.2 ml), n-butyl lithium (a 1.59N hexane solution, 320 μl) was added at -78°C, followed by stirring for 1 hour and then at 0°C for 30 minutes. The reaction mixture was cooled to -78°C and a carbon dioxide gas was introduced therein for 1 hour.

After the reaction mixture was heated to room temperature over 30 minutes, it was concentrated. To a solution of the resulting residue in N,N-dimethylformamide (6.0 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (177 mg, 510 μmol) was dissolved, followed by the addition
 of 1-(dimethylaminopropyl)-3-ethylcarbodiimide (98.0 mg,

511 μmol) and 1-hydroxybenzotriazole (69.0 mg, 511 μmol) at room temperature and then, diisopropylethylamine (185 μl , 1.06 mmol) at 0°C. After stirring overnight at room temperature, the reaction mixture was added with methylene chloride (20 ml) and a saturated aqueous solution (50 ml) of sodium bicarbonate, whereby the organic layer was separated. The resulting organic layer was extracted with methylene chloride (2 x 10 ml). The organic layers were combined, washed with water (50 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified twice by preparative thin-layer chromatography on a silica gel (methylene chloride : acetone : methanol = 10:5:1). The white solid thus obtained was dissolved in a 1N ethanol hydrochloride solution and the resulting solution was concentrated. After the addition of water, the mixture was concentrated again, whereby the title compound (74.7 mg) was obtained as a white solid.

IR(KBr) cm^{-1} : 3396, 2918, 2850, 2538, 1620, 1456, 1432, 1344, 1329, 1282, 1161, 955, 941, 729.

^1H -NMR (DMSO- d_6) δ : 2.68(1H, br d, $J=15.1\text{Hz}$), 2.78-2.92(1H, br), 2.85(3H, s), 3.04(4H, br s), 3.26(1H, br s), 3.52(1H, br s), 3.72(4H, br s), 4.20(1H, br d, $J=15.1\text{Hz}$), 4.43(1H, br d, $J=15.1\text{Hz}$), 6.92(1H, s), 7.71(1H, dd, $J=2.0, 8.8\text{Hz}$), 7.80(1H, d, $J=8.8\text{Hz}$),

8.15 (1H, d, J=8.8Hz), 8.23 (1H, s), 8.25 (1H, d, J=8.8Hz),
8.48 (1H, s), 11.64 (1H, br s).

MS (FAB) m/z: 474 [(M+H)⁺].

Elementary analysis for C₂₃H₂₄ClN₃O₄S·1.1HCl·1.7H₂O

5 Calculated: C, 50.72; H, 5.27; N, 7.71; Cl, 13.67; S, 5.89.

Found: C, 50.58; H, 5.39; N, 7.69; Cl, 13.94; S, 5.85.

[Example B-83] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride

10 To 6-(t-butoxycarbonyl)-2-[[4-(chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine (1.28 g, 2.24 mmol), a saturated ethanol hydrochloride solution (50 ml) was added at room temperature. The resulting mixture was stirred for 20
15 minutes, followed by concentration, whereby the title compound (1.26 g) was obtained as a white solid.

IR(KBr)cm⁻¹: 3396, 2924, 2615, 2544, 1957, 1655, 1610, 1473, 1454, 1425, 1448, 1336, 1286, 1157, 941, 731, 580.

¹H-NMR (DMSO-d₆) δ: 3.02 (2H, br t, J=5.3Hz),

20 3.05 (2H, t, J=6.4Hz), 3.42-3.49 (2H, br m), 3.52 (2H, br t, J=5.3Hz), 3.75 (2H, br t, J=5.3Hz), 4.33 (2H, br t, J=5.3Hz), 7.56 (1H, br d, J=8.3Hz), 7.89 (1H, d, J=8.3Hz), 7.89 (1H, dd, J=1.5, 8.8Hz), 7.98 (1H, dd, J=2.0, 8.8Hz), 8.34 (1H, d, J=8.8Hz), 8.43 (1H, s), 8.44 (1H, d, J=8.8Hz),
25 8.67 (1H, br s), 9.87 (2H, br s).

MS (FAB) m/z: 471 [(M+H)⁺, Cl³⁵].

Elementary analysis for $C_{23}H_{23}ClN_4O_3S \cdot 1.9HCl \cdot 0.9H_2O$

Calculated: C, 49.64; H, 4.84; Cl, 10.07; N, 18.48; S, 5.76.

Found: C, 49.64; H, 4.96; Cl, 10.01; N, 18.73; S, 5.93.

[Example B-84] 2-[[4-(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride

To a solution of 2-[[4-(chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine (174 mg) in methylene chloride (3.5 ml), triethylamine (95.6 μ l), acetic acid (58.9 μ l), formaldehyde (a 37% aqueous solution, 42.0 μ l) and sodium triacetoxymethylborohydride (110 mg) were added at room temperature, followed by stirring for 15 minutes. To the reaction mixture, a saturated aqueous solution (10 ml) of sodium bicarbonate and methylene chloride (10 ml) were added to separate the water layer. The resulting water layer was extracted with methylene chloride (10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on a silica gel (methylene chloride : methanol = 15:1). The white solid thus obtained was dissolved in a 1N aqueous hydrochloride in ethanol,

followed by concentration, whereby the title compound (170 mg) was obtained as a white solid.

IR(KBr) cm^{-1} : 3359, 2918, 2544, 1655, 1641, 1475, 1431, 1342, 1331, 1284, 1155, 953, 941, 727, 579.

5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 3.04 (3H, d, $J=3.9\text{Hz}$), 3.17 (2H, br s), 3.26 (2H, br s), 3.38-3.65 (2H, m), 3.68 (2H, br s), 3.39 (2H, br s), 4.40-4.70 (2H, m), 4.57 (2H, br s), 7.57 (1H, d, $J=7.8\text{Hz}$), 7.84-7.92 (2H, m), 7.98 (1H, d, $J=8.8\text{Hz}$), 8.33 (1H, d, $J=8.3\text{Hz}$), 8.42 (1H, s), 8.43 (1H, d, $J=8.8\text{Hz}$), 8.67 (1H, s), 11.86 (1H, br s).
10 MS (FAB) m/z : 485 [$(\text{M}+\text{H})^+$, Cl^{35}].

[Example B-85] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride

A saturated solution of hydrochloride in ethanol (25 ml) was added to 1,5-bis(*t*-butoxycarbonyl)-2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine (300 mg) at room temperature, followed by stirring for 1 hour. The reaction mixture was concentrated and water was added to the concentrate. The resulting mixture was concentrated under reduced pressure. To the residue, a saturated solution of hydrochloride in methanol (25 ml) was added at room temperature, followed by stirring for 1 hour. After concentration of the reaction mixture, water was added and the resulting mixture was concentrated under reduced pressure, whereby the title compound (200 mg) was obtained

as a white solid.

IR(KBr)cm⁻¹: 3290, 2918, 2762, 2559, 1614, 1483, 1454, 1381, 1340, 1323, 1244, 1155, 1147, 1136, 978, 955, 727, 575.

5 ¹H-NMR (DMSO-d₆) δ: 2.77(2H,br t,J=5.9Hz),
3.03(4H,t,J=5.3Hz), 3.30(2H,br t,J=5.9Hz), 3.73(4H,br
t,J=5.3Hz), 3.99(2H,br s), 6.32(1H,d,J=2.0Hz),
7.73(1H,dd,J=2.0,8.8Hz), 7.83(1H,dd,J=2.0,8.8Hz),
8.17(1H,d,J=8.8Hz), 8.25(1H,d,J=2.0Hz), 8.28(1H,d,J=8.8Hz),
10 8.50(1H,br s), 9.07(2H,br), 11.38(1H,br).

MS (FAB) m/z: 459 [(M+H)⁺, Cl³⁵].

Elementary analysis for C₂₂H₂₃ClN₄O₃S·1.1HCl·0.3H₂O

Calculated: C, 52.38; H, 4.94; N, 11.11; Cl, 14.76; S, 6.36.

15 Found: C, 52.48; H, 4.92; N, 11.07; Cl, 14.48; S, 6.65.

[Example B-86] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride

20 In methylene chloride (4.5 ml), 2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride (200 mg) was suspended, followed by the addition of triethylamine (125 μl), acetic acid (77.0 μl),

25 formaldehyde (a 37% aqueous solution, 56.1 μl) and sodium

triacetoxyborohydride (139 mg) at room temperature. The resulting mixture was stirred for 15 minutes. To the reaction mixture, a saturated aqueous solution (20 ml) of sodium bicarbonate and methylene chloride (10 ml) were added to separate the water layer. The resulting water layer was extracted with methylene chloride (2 x 10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (25 g of silica gel, methylene chloride : methanol = 10:1 → 7:1). The resulting solid was dissolved in a 1N aqueous hydrochloride in ethanol. After concentration of the resulting solution, water was added to the concentrate and the mixture was concentrated again, whereby the title compound (133 mg) was obtained as a white solid.

IR(KBr)cm⁻¹: 3213, 2918, 2650, 2530, 1604, 1585, 1508, 1491, 1456, 1342, 1331, 1157, 727, 579.

¹H-NMR (DMSO-d₆) δ: 2.72-2.86(1H,m), 2.83(3H,d,J=4.9Hz), 2.87-2.99(1H,m), 3.03(4H,br t,J=4.4Hz), 3.19-3.31(1H,m), 3.46-3.64(1H,m), 3.74(4H,br t,J=4.4Hz), 3.97(1H,dd,J=7.8,14.2Hz), 4.20(1H,br d,J=14.2Hz), 6.32(1H,d,J=2.4Hz), 7.72(1H,dd,J=2.4,8.8Hz), 7.82(1H,dd,J=2.0,8.8Hz), 8.16(1H,d,J=8.8Hz), 8.25(1H,d,J=2.0Hz), 8.27(1H,d,J=8.8Hz), 8.51(1H,br s), 10.84(1H,br s), 11.42(1H,br s).

MS (FAB) m/z : 473 [(M+H)⁺, Cl³⁵].

Elementary analysis for C₂₃H₂₅ClN₄O₃S·1.3HCl·0.7H₂O

Calculated: C, 51.83; H, 5.24; N, 10.51; Cl, 15.30; S, 6.02.

5 Found: C, 51.83; H, 5.37; N, 10.30; Cl, 15.35; S, 6.09.

[Example B-87] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5-ethyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride

10 In methylene chloride (3.0 ml), 2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride (149 mg) was suspended, followed by the addition of methanol (0.6 ml), triethylamine (82.5 μ l), acetic acid
15 (51.0 μ l, 891 μ mol), acetaldehyde (19.5 μ l) and sodium triacetoxyborohydride (74.0 mg) at room temperature. The resulting mixture was stirred for 15 minutes. To the reaction mixture, a saturated aqueous solution (30 ml) of sodium bicarbonate and methylene chloride (15 ml) were
20 added to separate the water layer. The resulting water layer was extracted with methylene chloride (2 x 10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by chromatography on
25 a silica gel column (30 g of silica gel, methylene

chloride : methanol = 10:1). The resulting white solid was dissolved in a 1N aqueous hydrochloride in ethanol (10 ml). After concentration of the resulting solution, water (30 ml) was added to the concentrate and the mixture was concentrated again, whereby the title compound (81.7 mg) was obtained as a white solid.

IR(KBr)cm⁻¹: 3386, 3226, 2918, 2586, 1603, 1585, 1491, 1454, 1427, 1344, 1331, 1163, 1136, 1078, 933, 727, 579.

¹H-NMR (DMSO-d₆) δ: 1.26(3H,t,J=7.3Hz), 2.72-2.82(1H,m), 2.86-3.00(1H,m), 3.02(4H,br s), 3.12-3.64(6H,m), 3.73(4H,br s), 3.96(1H,dd,J=7.8,14.1Hz), 4.22(1H,br d,J=14.1Hz), 6.31(1H,d,J=2.4Hz), 7.71(1H,br d,J=8.8Hz), 7.81(1H,br d,J=8.8Hz), 8.16(1H,d,J=8.8Hz), 8.23(1H,br s), 8.26(1H,d,J=8.8Hz), 8.50(1H,br s), 10.39(1H,br s), 11.40(1H,br s).

MS (FAB) m/z: 486 [(M+H)⁺, Cl³⁵].

Elementary analysis for C₂₄H₂₇ClN₄O₃S·1.2HCl·2.0H₂O

Calculated: C, 50.86; H, 5.73; N, 9.88; Cl, 13.76; S, 5.66.

Found: C, 51.11; H, 5.71; N, 9.58; Cl, 13.60; S, 5.66.

[Example B-88] 5-(t-Butoxycarbonyl)-2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine

In methylene chloride (15 ml), 2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride (780 mg) was suspended, followed by the addition of a

saturated aqueous solution (15 ml) of sodium bicarbonate and di-*t*-butyl dicarbonate (506 ml) at room temperature. The resulting mixture was stirred for 1 hour. To the reaction mixture, water (30 ml) and methylene chloride (30 ml) were added to separate the water layer. The resulting water layer was extracted with methylene chloride (2 x 20 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (75 g of silica gel, methylene chloride : acetone = 8:1 → 2:1). The resulting white solid was dissolved in a 1N aqueous hydrochloride in ethanol. After concentration of the resulting solution, water was added to the concentrate and the mixture was concentrated again, whereby the title compound (641 mg) was obtained as a white solid.

¹H-NMR (CDCl₃) δ: 1.46(9H,s), 2.61(2H,br s), 3.12(4H,br t,J=4.9Hz), 3.66(2H,br s), 3.90(4H,br t,J=4.9Hz), 4.36(2H,br s), 6.19(1H,d,J=2.0Hz), 7.57(1H,dd,J=1.7,9.0Hz), 7.76(1H,br d,J=8.8Hz), 7.86-7.97(3H,m), 8.29(1H,br s), 9.24(1H,br s).

[Example B-89] 5-(*t*-Butoxycarbonyl)-2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-*c*]pyridine

To a solution of 5-(*t*-butoxycarbonyl)-2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-

4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine (33.0 mg) in N,N-dimethylformamide (15 ml), sodium hydride (60% in oil, 3.5 mg) was added at 0°C. After stirring for 10 minutes, methyl iodide (4.5 μ l) was added and the resulting mixture was stirred at 0°C for 1 hour. To the reaction mixture, a saturated aqueous solution (10 ml) of ammonium chloride, methylene chloride (20 ml) and water (30 ml) were added to separate the organic layer. The resulting water layer was extracted with methylene chloride (10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on a silica gel (methylene chloride : acetone = 9:1), whereby the title compound (32.3 mg) was obtained as a colorless, transparent viscous substance.

¹H-NMR (CDCl₃) δ : 1.46(9H,s), 2.58(2H,br s), 3.12(4H,br t, J=4.5Hz), 3.50(3H,s), 3.68(2H,br s), 3.84(4H,br t, J=4.5Hz), 4.32(2H,br s), 6.02(1H,s), 7.58(1H,dd, J=2.0, 8.8Hz), 7.77(1H,dd, J=1.7, 8.5Hz), 7.88-7.97(3H,m), 8.32(1H,br s).

[Example B-90] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride

To 5-(t-butoxycarbonyl)-2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine (280 mg), a saturated

solution hydrochloride in ethanol (25 ml) was added at room temperature, followed by stirring for 1 hour. The reaction mixture was then concentrated. Water (10 ml) was added to the concentrate, followed by concentration under reduced pressure, whereby the title compound (210 mg) was obtained as a white solid.

IR(KBr) cm^{-1} : 3381, 2918, 2748, 1622, 1583, 1495, 1454, 1342, 1331, 1248, 1163, 1136, 953, 935, 879, 726, 579, 476.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.81(2H, br t, $J=5.6\text{Hz}$), 3.05(4H, br s), 3.35(2H, br t, $J=5.6\text{Hz}$), 3.42(3H, s), 3.69(4H, br s), 3.97(2H, br s), 6.18(1H, s), 7.73(1H, dd, $J=2.0, 8.8\text{Hz}$), 7.83(1H, dd, $J=2.0, 8.8\text{Hz}$), 8.18(1H, d, $J=8.8\text{Hz}$), 8.27(1H, br s), 8.28(1H, d, $J=8.8\text{Hz}$), 8.50(1H, br s), 9.34(1H, br d, $J=27.4\text{Hz}$).

MS (FAB) m/z : 473 [$(M+H)^+$, Cl^{35}].

Elementary analysis for $\text{C}_{23}\text{H}_{25}\text{ClN}_4\text{O}_3\text{S} \cdot 1.4\text{HCl} \cdot 1.2\text{H}_2\text{O}$

Calculated: C, 50.63; H, 5.32; N, 10.27; Cl, 15.59; S, 5.88.

Found: C, 50.71; H, 5.53; N, 10.14; Cl, 15.53; S, 5.90.

[Example B-91] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1,5-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride

In methylene chloride (10 ml), 2-[[4-(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride (170 mg) was suspended, followed by the

addition of methanol (10 ml), triethylamine (100 μ l),
acetic acid (62.0 μ l), formaldehyde (a 37% aqueous
solution, 46.5 μ l) and sodium triacetoxyborohydride (115
mg) at room temperature. The resulting mixture was stirred
5 for 30 minutes. To the reaction mixture, a saturated
aqueous solution (50 ml) of sodium bicarbonate and
methylene chloride (30 ml) were added to separate the water
layer. The water layer thus obtained was extracted with
methylene chloride (2 x 10 ml). The organic layers were
10 combined, dried over anhydrous sodium sulfate and
concentrated under reduced pressure. The residue was
purified by chromatography on a silica gel column (30 g of
silica gel, methylene chloride : methanol = 10:1 \rightarrow 7:1).
The resulting white solid was dissolved in a 1N aqueous
15 hydrochloride in ethanol. After the concentration of the
resulting solution, water was added to the concentrate and
the resulting mixture was concentrated again, whereby the
title compound (162 mg) was obtained as a white solid.
IR(KBr)cm⁻¹: 3396, 2924, 2663, 2586, 1622, 1581, 1456,
20 1342, 1329, 1248, 1163, 1136, 955, 937, 727, 579.
¹H-NMR (DMSO-d₆) δ : 2.77-3.00(5H,m), 3.06(4H,br s), 3.23-
3.37(1H,m), 3.43(3H,s), 3.55-3.65(1H,m), 3.69(4H,br s),
3.90-4.03(1H,m), 3.93(3H,s), 4.19(1H,br d,J=11.7Hz),
6.18(1H,s), 7.74(1H,dd,J=2.0,8.8Hz),
25 7.83(1H,dd,J=2.0,8.8Hz), 8.18(1H,d,J=8.8Hz), 8.27(1H,br s),

8.28 (1H, d, J=8.8 Hz), 8.51 (1H, br s), 11.00 (1H, br s).

MS (FAB) m/z: 487 [(M+H)⁺, Cl³⁵].

Elementary analysis for C₂₄H₂₇ClN₄O₃S·1.4HCl·1.4H₂O

Calculated: C, 51.18; H, 5.58; N, 9.95; Cl, 15.11; S, 5.69.

5 Found: C, 51.09; H, 5.83; N, 9.78; Cl, 15.37; S, 5.79.

[Example B-92] 2-(N-Methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-trimethylsilylethynylbenzo[b]thien-2-yl)sulfonyl]piperazine

In N,N-dimethylformamide (5 ml) was dissolved 3-(N-methylcarbamoyl)-1-[(6-trimethylsilylethynylbenzo[b]thien-2-yl)sulfonyl]piperazine (218 mg), followed by the addition of lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate (188 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (240 mg) and 15 1-hydroxybenzotriazole (68 mg). The resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with methylene chloride, washed with water (twice) and then with a saturated aqueous solution of sodium bicarbonate. After drying over anhydrous sodium sulfate, the solvent was distilled off under reduced 20 pressure. The residue was purified by chromatography on a silica gel column (methanol : methylene chloride = 3:97 → 5:95 → 7:93), whereby the title compound (90 mg) was obtained.

25 MS (FAB) m/z: 616 (M+H)⁺.

[Example B-93] 4-[(6-Ethynylbenzo[b]thien-2-yl)sulfonyl]-2-[N-methylcarbamoyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In a mixed solvent of tetrahydrofuran (0.5 ml) and methanol (0.5 ml) was dissolved 2-(N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-trimethylsilylethynylbenzo[b]thien-2-yl)sulfonyl]piperazine (90 mg), followed by the addition of a 1N aqueous solution (0.3 ml) of sodium hydroxide. The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was made weakly acidic with a saturated aqueous solution of ammonium chloride and then made weakly alkaline with a saturated aqueous solution of sodium bicarbonate. The solution was extracted (four times) with methylene chloride. The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by preparative thin-layer chromatography (methanol : methylene chloride = 1:9). Similar reaction and post treatment were repeated three times and the purified products were combined, followed by purification through Sephadex LH-20 (elution with methanol). The amorphous substance thus obtained was dissolved in methylene chloride. Hexane was added dropwise to the resulting solution, whereby the title compound (82 mg) was obtained as a light gray solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.49(3H,s), 2.80-2.90(10H,m), 3.15-3.18(1H,m), 3.22(1H,s), 3.53-3.62(1H,m), 3.67(1H,s), 4.49(1H,d,J=12.2Hz), 4.65, 5.74(total 1H,each d,J=13.7Hz), 5.26, 6.18(total 1H,each s), 6.45, 6.49(total 1H,each s),
 5 7.54(1H,d,J=8.3Hz), 7.80(1H,s), 7.82(1H,d,J=8.3Hz),
 7.97(1H,s).

MS (FAB) m/z : 544 ($\text{M}+\text{H}$) $^+$.

[Example B-94] 1-[(6-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[[methyl]piperazine
 10 (morpholin-4-yl)carbonyl]methyl]piperazine

In methylene chloride (5 ml) was dissolved 1-(tert-butoxycarbonyl)-4-[(5-chloroindol-2-yl)sulfonyl]-2-[[methyl]piperazine (930 mg),
 15 followed by the addition of trifluoroacetic acid (2 ml). The resulting mixture was stirred at room temperature for 30 minutes. A saturated aqueous solution of sodium bicarbonate was added and the resulting mixture was extracted with methylene chloride. The organic layer was
 20 dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in N,N-dimethylformamide (10 ml), followed by the addition of lithium 6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate (695 mg),
 25 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (506 mg) and 1-hydroxybenzotriazole (119 mg). The

resulting mixture was stirred overnight at room temperature. A saturated aqueous solution of sodium bicarbonate was added and the resulting mixtures was extracted with methylene chloride. The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 1:1), whereby the title compound (585 mg) was obtained as an orange foam.

¹H-NMR (CDCl₃) δ: 1.48 (9H, s), 2.58-3.96 (19H, m), 4.60-6.02 (4H, m), 6.98 (1H, s), 7.27 (1H, d, J=9.0Hz), 7.38 (1H, d, J=9.0Hz), 7.64 (H, s), 10.39 (1H, s).

[Example B-95] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methylsulfonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[(morpholin-4-yl)carbonyl]methyl]piperazine

In methylene chloride (5 ml) was dissolved 1-[(6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[[(morpholin-4-yl)carbonyl]methyl]piperazine (585 mg), followed by the addition of trifluoroacetic acid (2 ml). The resulting mixture was stirred at room temperature for 30 minutes. A saturated aqueous solution of sodium bicarbonate was added and the resulting mixture was extracted with methylene chloride (to which N,N-dimethylformamide was added in a small amount). The organic layer was dried over anhydrous sodium sulfate and

distilled under reduced pressure to remove the solvent. To the residue was added a 1N aqueous hydrochloride in ethanol (1 ml) and the solvent was distilled off under reduced pressure, whereby the hydrochloride (585 mg, containing two molecules of N,N-dimethylformamide). A 100 mg portion of the resulting hydrochloride was added to methylene chloride (3 ml), followed by the addition of triethylamine (0.5 ml) and methanesulfonyl chloride (20 mg). The resulting mixture was stirred at room temperature for 2 hours. A saturated aqueous solution of sodium bicarbonate was added to the reaction mixture. The resulting mixture was extracted with methylene chloride. The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by preparative thin-layer chromatography (methylene chloride : methanol = 9:1). The solid thus obtained was dissolved in methylene chloride, followed by the addition of ether for crystallization, whereby the title compound (34.2 mg) was obtained as a white solid.

¹H-NMR (DMSO-d₆) δ: 2.33-3.57(20H,m), 3.72-3.79(2H,m), 4.38, 5.39(total 1H,each d,J=12.2,13.7Hz), 4.55(2H,s), 5.06, 5.82(total 1H,each br s), 7.02(1H,s), 7.30(1H,d,J=8.8Hz), 7.47(1H,d,J=8.8Hz), 7.76(1H,s), 12.41(1H,s).

MS (FAB) m/z: 671 (M+H)⁺.

[Example B-96] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-(N-

methylcarbamoyl)-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine trifluoroacetate

In N,N-dimethylformamide (50 ml) were dissolved 6-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylic acid (530 mg), 4-[(5-chloronaphthalen-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]piperazine hydrochloride (527 mg) and 1-hydroxybenzotriazole monohydrate (200 mg) and 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (324 mg), followed by the addition of triethylamine (0.18 ml). The resulting mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure. Methylene chloride was added to the residue and the resulting mixture was washed with water and saturated aqueous NaCl solution, each once. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : methanol = 100:1), whereby pale yellow foam (577 mg) was obtained. The resulting foam was dissolved in methylene chloride (3 ml), followed by the addition of trifluoroacetic acid (6 ml). The resulting mixture was concentrated under reduced pressure. The precipitate so formed was collected by filtration while being washed with diethyl ether, whereby the title compound (596 mg) was obtained as colorless foam.

¹H-NMR (DMSO-d₆) δ: 2.53-2.62 (3H,m), 2.63-2.74 (1H,m), 2.90-3.06 (2H,m), 3.12-3.22 (0.5H,m), 3.39-3.59 (1.5H,s), 3.68-3.77 (1H,m), 4.28 (1H,d,J=11.7Hz), 4.28-4.50 (1.5H,m), 4.97 (0.5H,br s), 5.44 (0.5H,d,J=13.2Hz), 6.13 (0.5H,br s), 7.72 (1H,dd,J=8.8,2.0Hz), 7.80 (1H,d,J=8.8Hz), 8.07-8.18 (2H,m), 8.22-8.27 (2H,m), 8.50 (1H,s), 9.16-9.40 (1H,m). MS (FAB) m/z: 534 [(M+H)⁺, Cl³⁵], 536 [(M+H)⁺, Cl³⁷].

[Example B-97] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6-methylsulfonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-95, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.61-2.87 (1H,m), 2.88 (6H,br s), 2.89-3.24 (3H,m), 3.45-3.90 (4H,m), 4.43-4.60 (3H,m), 4.74, 5.21 (total 1H,each br s), 5.60-6.09 (total 1H,m), 6.30, 6.42 (total 1H,br s), 7.58 (1H,d,J=7.6Hz), 7.80 (1H,d,J=9.0Hz), 7.89-7.91 (3H,m), 8.35 (1H,s). MS (FAB) m/z: 612 (M+H)⁺.

[Example B-98] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-dimethylaminosulfonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[morpholin-4-yl)carbonyl]methyl]piperazine

In the same manner as in Example B-95, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.60-3.79 (25H,m), 4.38, 5.37 (total

1H, each d, J=13.5, 14.5 Hz), 4.53 (2H, s), 5.04, 5.75 (total
 1H, each br), 7.02 (1H, s), 7.30 (1H, dd, J=8.8, 2.0 Hz),
 7.47 (1H, d, J=8.8 Hz), 7.76 (1H, s), 12.41 (1H, s).
 MS (FAB) m/z: 700 (M+H)⁺.

5 [Example B-99] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-
 methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 yl)carbonyl]-2-[[(morpholin-4-yl)carbonyl]methyl]piperazine
 hydrochloride

To an ethanol solution (50 ml) of 1-(tert-
 10 butoxycarbonyl)-4-[(5-chloroindol-2-yl)sulfonyl]-2-
 [[(morpholin-4-yl)carbonyl]methyl]piperazine (710 mg) was
 added a saturated ethanol hydrochloride solution (20 ml) at
 room temperature. The resulting mixture was stirred for 3
 hours. After concentration of the reaction mixture under
 15 reduced pressure, diethyl ether and ethanol were added to
 precipitate crystals. The resulting crystals were
 collected by filtration, washed with ethanol and then dried
 under reduced pressure. The crystals were dissolved in
 N,N-dimethylformamide to form an N,N-dimethylformamide
 20 solution (50 ml), followed by the addition of 1-
 hydroxybenzotriazole (68.8 mg), 1-(3-dimethylaminopropyl-3-
 ethylcarbodiimide hydrochloride (115.4 mg), lithium 6-
 methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-
 carboxylate (189.0 mg) and N-methylmorpholine (140.5 mg) at
 25 room temperature. The resulting mixture was stirred at
 room temperature for 19 hours. The reaction solvent was

distilled off under reduced pressure. Distilled water and ethyl acetate were added to the residue and the water layer was extracted three times. The organic layers were combined, washed four times with distilled water, dried
 5 over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to chromatography on a silica gel column (methanol : ethyl acetate = 1:50). Diethyl ether and methylene chloride were added to the purified product to precipitate crystals. The
 10 resulting crystals were collected by filtration, followed by washing with diethyl ether. A 1N aqueous hydrochloric acid in ethanol (0.5 ml) and a small amount of distilled water were added. The solvent was then distilled off under reduced pressure. The residue was dried under heat at 60°C
 15 under reduced pressure, whereby the title compound (187 mg) was obtained as a yellow amorphous solid.

MS (FAB⁺) m/z: 607 [(M+H)⁺, Cl³⁵], 609 [(M+H)⁺, Cl³⁷].

¹H-NMR (DMSO-d₆) δ: 2.66-2.89(1H,m), 2.99(3H,s), 3.03-
 3.29(2H,m), 3.34-3.46(1H,m), 3.52-3.92(8H,m), 4.42-
 20 4.53(1.5H,m), 4.73-4.81(1H,m), 5.10-5.17(0.5H,m), 5.39-
 5.47(1H,m), 5.82-5.92(0.5H,m), 7.12(1H,br),
 7.41(1H,dd,J=2.0,8.8Hz), 7.58(1H,d,J=8.8Hz), 7.87(1H,br),
 12.57(1H,s).

[Example B-100] 2-(Carbamoylmethyl)-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-98, the title compound was obtained.

MS (FAB⁺) m/z: 537 [(M+H)⁺, Cl³⁵], 539 [(M+H)⁺, Cl³⁷].

¹H-NMR (DMSO-d₆) δ: 1.00-1.08 (1H,m), 2.65-2.68 (1H,m), 2.88-
 5 2.94 (2H,m), 3.00-3.12 (1H,m), 3.27-3.46 (3H,m), 3.62-
 3.73 (1H,m), 4.32-4.39 (1H,m), 5.04-5.37 (1H,m), 6.83-
 6.86 (1H,m), 7.01 (1H,s), 7.27-7.33 (1H,m),
 7.46 (1H,d,J=8.5Hz), 7.76 (1H,s), 12.42 (1H,s).

[Example B-101] 1-[(5-Chloroisoindolin-2-yl)sulfonyl]-4-
 10 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 yl)carbonylpiperazine hydrochloride

In the same manner as in Example B-62, the title compound was obtained.

MS (FAB⁺) m/z: 482 [(M+H)⁺, Cl³⁵], 484 [(M+H)⁺, Cl³⁷].

15 ¹H-NMR (CDCl₃) δ: 2.93 (3H,s), 3.08-3.19 (1H,m), 3.28-
 3.40 (8H,m), 3.40-3.53 (1H,br), 3.68-3.77 (2H,br), 4.28-
 4.46 (2H,m), 4.63-4.65 (4H,m), 7.33 (1H,d,J=8.3Hz),
 7.37 (1H,dd,J=2.0,8.3Hz), 7.41 (1H,s).

[Example B-102] 1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(6-
 20 methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 yl)carbonylpiperazine

A saturated solution of hydrochloride in ethanol (8.0 ml) was added to 1-(tert-butoxycarbonyl)-4-[(6-methyl-
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 25 yl)carbonylpiperazine (300 mg). After stirring for 1

hour, the reaction mixture was concentrated under reduced pressure. To the residue were added N,N-dimethylformamide (8.0 ml) and 1-phenylsulfonyl-5-trimethylsilylethynylindol-2-sulfonyl chloride (450 mg) at room temperature, followed
5 by the addition of diisopropylethylamine (860 μ l) at 0°C. After stirring at room temperature for 1 hour, the reaction mixture was concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone : methanol = 30:10:1
10 \rightarrow 10:10:1), whereby 4-[(6-methyl-4,5,6,7-tetrahydrothizolo[5,4-c]pyridin-2-yl)carbonyl]-1-[(1-phenylsulfonyl-5-trimethylsilylethynylindol-2-yl)carbonyl]piperazine (123 mg) was obtained as a colorless viscous substance. The resulting substance was dissolved
15 in tetrahydrofuran (3.0 ml), followed by the addition of methanol (3.0 ml) and potassium hydroxide (22.5 mg) at room temperature. After stirring for 2 hours, a saturated aqueous solution (10 ml) of ammonium chloride was added. A saturated aqueous solution (15 ml) of sodium bicarbonate
20 and methylene chloride (10 ml) were added and the mixture was separated into layers. The water layer was extracted with methylene chloride (10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue
25 was purified by preparative thin-layer chromatography (methylene chloride : acetone : methanol = 40:10:1) using

silica gel, whereby the title compound (39.4 mg) was obtained as a colorless solid. The resulting compound was dissolved in methylene chloride, methanol and water. The resulting solution was concentrated under reduced pressure, followed by drying, whereby the title compound was obtained as a colorless solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.49(3H,s), 2.81(2H,t,J=5.5Hz), 2.90(2H,t,J=5.5Hz), 3.04(1H,s), 3.22(4H,br s), 3.68(2H,s), 3.88(2H,br s), 4.57(2H,br s), 7.00(1H,s), 7.37(1H,d,J=8.6Hz), 7.47(1H,dd,J=8.6,1.5Hz), 7.86(1H,s), 8.88(1H,br s).

MS (FAB) m/z : 470 ($\text{M}+\text{H}$) $^+$.

[Example B-103] 2-(*N*-Methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridin-2-yl)carbonyl]-4-[(1-phenylsulfonyl-5-trimethylsilylethynylindol-2-yl)sulfonyl]piperazine

A saturated solution of hydrochloride in methanol (20 ml) was added to 4-(tert-butoxycarbonyl)-2-(*N*-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridin-2-yl)carbonyl]piperazine (410 mg) at room temperature. After stirring for 1 hour, the reaction mixture was concentrated under reduced pressure. To the residue were added methylene chloride (15 ml) and 1-phenylsulfonyl-5-trimethylsilylethynylindol-2-sulfonyl chloride (450 mg) at room temperature, followed by the addition of diisopropylethylamine (590 μl) at room

temperature. After stirring for 12 hours,
 diisopropylethylamine (590 μ l) was added again at room
 temperature. The resulting mixture was stirred at room
 temperature for 4 hours. A saturated aqueous solution (50
 5 ml) of sodium bicarbonate and methylene chloride (50 ml)
 were added to the reaction mixture and the mixture was
 separated into layers. The water layer was extracted with
 methylene chloride (2 x 20 ml). The organic layers were
 combined, dried over anhydrous sodium sulfate and distilled
 10 under reduced pressure to remove the solvent. The residue
 was purified by chromatography on a silica gel column
 (methylene chloride : methanol = 20:1), whereby the title
 compound (389 mg) was obtained as a colorless transparent
 glassy substance.

15 $^1\text{H-NMR}$ (CDCl_3) δ : 0.25 (9H, s), 2.50 (3H, d, $J=8.3\text{Hz}$), 2.65-
 3.02 (8H, m), 3.05-3.30 (2H, m), 3.70 (2H, br s),
 4.13 (1H, d, $J=13.4\text{Hz}$), 4.40 (1H, d, $J=13.4\text{Hz}$),
 4.67 (1/2H, d, $J=13.4\text{Hz}$), 5.24 (1/2H, br s),
 5.66 (1/2H, d, $J=14.0\text{Hz}$), 6.08 (1/2H, br s), 6.39 (1H, br s),
 20 7.41 (2H, t, $J=7.7\text{Hz}$), 7.47-7.63 (3H, m), 7.71 (1H, s),
 8.02 (2H, d, $J=7.8\text{Hz}$), 8.18 (1H, d, $J=8.8\text{Hz}$).
 MS (FAB) m/z : 739 ($\text{M}+\text{H}$) $^+$.

[Example B-104] 4-[(5-Ethynylindol-2-yl)sulfonyl]-2-(*N*-
 methylcarbamoyl)-1-[(6-methyl-4,5,6,7-
 25 tetrahydrothiazolo[5,4-*c*]pyridin-2-yl)carbonyl]piperazine

In tetrahydrofuran (5.0 ml) was dissolved 2-[(*N*-

methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(1-phenylsulfonyl-5-trimethylsilylethynylindol-2-yl)carbonyl]piperazine (350 mg), followed by the addition of methanol (5.0 ml) and potassium hydroxide (102 mg) at room temperature. After stirring for 4 hours, a saturated aqueous solution (50 ml) of sodium bicarbonate and methylene chloride (50 ml) were added to the reaction mixture to separate the mixture into layers. The water layer was extracted with methylene chloride (50 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified twice by chromatography on a silica gel column (methylene chloride : methanol = 20:1), whereby the title compound (126 mg) was obtained as a colorless solid. The resulting solid was dissolved in methylene chloride, methanol and water, followed by concentration under reduced pressure and drying, whereby the title compound was obtained as a colorless solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.51 (3H, s), 2.75-3.30 (11H, m), 3.58-3.85 (3H, m), 4.50-4.70 (2H, m), 5.25 (1/2H, brs), 5.64 (1/2H, d, $J=11.5\text{Hz}$), 6.10 (1/2H, br s), 6.53 (1/2H, br s), 7.10 (1H, s), 7.43 (2H, s), 7.85 (1H, s), 10.78 (1H, d, $J=9.5\text{Hz}$).
MS (FAB) m/z : 527 ($\text{M}+\text{H}$) $^+$.

[Example B-105] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine-2-

yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-62, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.92(3H,s), 3.04-3.28(6H,m), 3.35-
 5 3.90(4H,m), 4.12-4.70(4H,m), 7.69(1H,dd,J=8.8,2.0Hz),
 7.82(1H,dd,J=8.8,2.0Hz), 8.14(1H,d,J=8.8Hz), 8.21(1H,s),
 8.25(1H,dd,dd,J=8.8,2.0Hz), 8.50(1H,s), 11.27(1H,br s).
 MS (FAB) m/z: 491 [(M+H)⁺, Cl³⁵], 493 [(M+H)⁺, Cl³⁷].

[Example B-106] 4-[(5-Chloronaphthalen-2-yl)sulfonyl]-2-
 10 (N-methylcarbamoyl)-1-[(5-methyl-4,5,6,7-
 tetrahydrothiazolo[4,5-c]pyridin-2-yl)carbonyl]piperazine
 hydrochloride

In the same manner as in Example B-62, the title compound was obtained.

15 ¹H-NMR (DMSO-d₆) δ: 2.43-2.81(5H,m), 2.89-2.95(4H,m), 3.22-
 3.80(6H,m), 4.16-4.65(2.5H,m), 5.01(0.5H,s), 5.36-
 5.45(0.5H,m), 6.06(0.5H,br s), 7.00(1H,s),
 7.29(1H,d,J=8.8Hz), 7.48(1H,d,J=8.8Hz), 7.75(1H,s), 11.25-
 11.40(1H,m), 12.43(1H,s).

20 MS (FAB) m/z: 537 [(M+H)⁺, Cl³⁵], 539 [(M+H)⁺, Cl³⁷].

[Example B-107] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-
 methylcarbamoyl)-1-[(5-isopropyl-4,5,6,7-
 tetrahydrothiazolo[4,5-c]pyridin-2-yl)carbonyl]piperazine
 hydrochloride

25 In the same manner as in Example B-62, the title

compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.31-1.40 (6H,m), 2.38-2.75 (5H,m), 3.10-3.80 (8H,m), 4.22-4.50 (2.5H,m), 4.97 (1/2H,br s), 5.35-5.49 (1/2H,m), 6.13 (1/4H,br s), 6.19 (1/4H,br s),
 5 7.70 (1H,d,J=8.8Hz), 7.79 (1H,d,J=8.8Hz), 8.09-8.28 (4H,m),
 8.49 (1H,s), 10.80-11.34 (1H,m).

MS (FAB) m/z: 576 [(M+H)⁺, Cl³⁵], 578 [(M+H)⁺, Cl³⁷].

[Example B-108] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(thiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

10 In the same manner as in Example B-62, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.20 (4H,br s), 3.84 (2H,br s),
 4.35 (2H,br s), 7.28 (1H,dd,J=8.8,2.5Hz),
 7.47 (1H,dd,J=8.8,2.0Hz), 7.74 (1H,d,J=2.0Hz),
 15 8.05 (1H,d,J=5.4Hz), 8.67 (1H,d,J=5.4Hz), 9.44 (1H,s),
 12.41 (1H,s).

MS (FAB) m/z: 462 [(M+H)⁺, Cl³⁵], 464 [(M+H)⁺, Cl³⁷].

[Example B-109] 2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-
 20 c]pyridinium iodide

In the same manner as in Example B-62, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.14-3.28 (4H,m), 3.86 (2H,br s),
 4.29 (2H,br s), 4.49 (3H,s), 7.04 (1H,s),
 25 7.30 (1H,dd,J=8.8,2.0Hz), 7.48 (1H,d,J=8.8Hz), 7.76 (1H,s),

8.72 (1H, d, J=6.8Hz), 9.00 (1H, d, J=6.8Hz), 9.94 (1H, s),
12.44 (1H, br s).

MS (FAB) m/z: 476, 478.

[Example B-110] 1-[(6-tert-Butoxycarbonyl-7-methyl-
5 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-
[(5-chloroindol-2-yl)sulfonyl]-2-(N-
methylcarbamoyl)piperazine hydrochloride

In the same manner as in Example B-62, the title
compound was obtained.

10 ¹H-NMR (DMSO-d₆) δ: 1.38 (3H, d, J=6.6Hz), 1.42 (9H, s), 2.55-
2.80 (5H, m), 3.31 (3H, s), 3.46-3.56 (1/2H, m), 3.61-3.72 (1H, m),
3.81-3.90 (1H, m), 4.18-4.29 (2H, m), 4.43-4.48 (1/2H, m), 4.91-
5.05 (1H, m), 5.26-5.45 (1H, m), 6.15-6.25 (2H, m), 6.98-
7.03 (1H, m), 7.26-7.33 (1H, m), 7.41-7.50 (1H, m), 7.73-
15 7.80 (1H, m), 8.02-8.17 (1H, m), 12.40 (1H, s).

MS (FAB) m/z: 637 [(M+H)⁺, Cl³⁵], 639 [(M+H)⁺, Cl³⁷].

[Example B-111] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-
methylcarbamoyl)-1-[(7-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
20 trifluoroacetate

In the same manner as in Example B-35, the title
compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.55 (3H, d, J=6.4Hz), 2.28-2.76 (5H, m),
2.88-3.10 (2H, m), 3.25-3.65 (1H, m), 4.20-4.30 (1H, m), 4.40-
25 4.50 (1/2H, m), 4.83 (1H, br s), 4.92-5.02 (1/2H, m), 5.40-

5.50 (1/2H,m), 6.13 (1/2H,s), 7.00 (1H,s), 7.30 (1H,d,J=8.8Hz),
7.46 (1H,d,J=8.8Hz), 7.76 (1H,s), 8.06-8.14 (1H,m), 8.93-
9.62 (2H,m), 12.40 (1H,s).

MS (FAB) m/z: 537 [(M+H)⁺, Cl³⁵], 539 [(M+H)⁺, Cl³⁷].

5 [Example B-112] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6,7-
dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]-2-(N-methylcarbamoyl)piperazine hydrochloride

In the same manner as in Example B-32, the title
compound was obtained.

10 ¹H-NMR (DMSO-d₆) δ: 1.40-1.70 (3H,m), 2.40-2.80 (4H,m),
2.92 (3H,br s), 3.00-3.25 (2H,m), 3.40-3.80 (1H,m), 4.19-
4.30 (1H,m), 4.39-4.50 (1/2H,m), 4.66-4.82 (1/2H,br s),
5.00 (1/2H,br s), 5.40-5.55 (1/2H,m), 5.73 (1/2H,br s),
6.17 (1/2H,br s), 7.00 (1H,s), 7.30 (1H,d,J=8.8Hz),
15 7.46 (1H,d,J=8.8Hz), 7.76 (1H,s), 8.05-8.20 (1H,m),
12.41 (1H,s).

MS (EI) m/z: 550 (M⁺, Cl³⁵), 552 (M⁺, Cl³⁷).

[Example B-113] 2-[N-[(5-Acetoxy-4-oxo-4H-pyran-2-
yl)methyl]carbamoyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-
20 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazine

In the same manner as in Example B-62, the title
compound was obtained.

¹H-NMR (DMSO-d₆ at 100°C) δ: 2.22 (3H,s), 2.38 (3H,s), 2.65-
25 2.89 (8H,m), 3.64 (2H,s), 3.70 (1H,d,J=11.0Hz),

4.28 (1H, d, J=12.4Hz), 6.30 (1H, s), 6.98 (1H, s),
 7.26 (1H, dd, J=9.2, 1.8Hz), 7.46 (1H, d, J=9.2Hz),
 7.70 (1H, d, J=1.8Hz), 8.28 (1H, s), 8.51 (1H, s), 12.00 (1H, br s).
 MS (FAB) m/z: 689 [(M+H)⁺, Cl³⁵], 691 [(M+H)⁺, Cl³⁷].

5

[Example B-114] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[N-[(5-hydroxy-4-oxo-4H-pyran-2-yl)methyl]carbamoyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

10 In the same manner as in Example B-23, the title compound was obtained.

¹H-NMR (DMSO-d₆ at 100°C) δ: 2.71-2.84 (1H, m), 2.90 (3H, s),
 3.00 (1H, dd, J=12.2, 4.3Hz), 3.06-3.28 (4H, m), 3.54 (2H, br s),
 3.74 (1H, d, J=12.0Hz), 4.09-4.28 (4H, m), 4.52 (2H, br s),
 7.00 (1H, d, J=1.2Hz), 7.29 (1H, dd, J=9.2, 1.8Hz),
 7.50 (1H, d, J=9.2Hz), 7.73 (1H, d, J=1.8Hz), 7.91 (1H, s),
 8.60 (1H, s), 12.14 (1H, br s).

15

MS (FAB) m/z: 647 [(M+H)⁺, Cl³⁵], 649 [(M+H)⁺, Cl³⁷].

[Example B-115] N-[[4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]acetyl]methanesulfonamide hydrochloride

20

In the same manner as in Example B-62, the title compound was obtained.

25

¹H-NMR (DMSO-d₆) δ: 2.61-3.10 (8H, m), 3.15 (3H, s), 3.34-

3.81 (4H,m), 3.90-4.48 (2.5H,m), 4.60-4.72 (1H,m),
 5.10 (0.5H,br s), 5.29-5.39 (0.5H,m), 5.80-6.00 (0.5H,m),
 7.02 (1H,s), 7.30 (1H,d,J=8.8Hz), 7.48 (1H,d,J=8.8Hz),
 7.75 (1H,s), 11.45-11.70 (1H,m), 11.85-12.00 (1H,m),
 5 12.46 (1H,br s).

MS (FAB) m/z: 615 [(M+H)⁺, Cl³⁵], 617 [(M+H)⁺, Cl³⁷].

[Example B-116] N-[[1-[(6-tert-Butoxycarbonyl-4,5,6,7-
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-
 chloroindol-2-yl)sulfonyl]piperazin-2-
 10 yl]acetyl]methanesulfonamide

In the same manner as in Example B-62, the title
 compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.40 (9H,s), 2.62-2.93 (6H,m), 3.09-
 3.20 (3H,m), 3.40-3.50 (0.5H,m), 3.60-3.78 (4.5H,m), 4.35-
 15 4.43 (0.5H,m), 4.61 (2H,s), 5.07-5.14 (0.5H,m), 5.30-
 5.40 (0.5H,m), 5.90-6.00 (0.5H,m), 7.03 (1H,s),
 7.29 (1H,dd,J=8.8,2.0Hz), 7.45 (1H,d,J=8.8Hz), 7.74 (1H,s),
 11.84 (1H,br s), 12.39 (1H,br s).

MS (FAB) m/z: 701 [(M+H)⁺, Cl³⁵], 703 [(M+H)⁺, Cl³⁷].

20 [Example B-117] N-[[4-[(5-Chloroindol-2-yl)sulfonyl]-1-
 [(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 yl)carbonyl]piperazin-1-yl]acetyl]methanesulfonamide
 trifluoroacetate

In the same manner as in Example B-35, the title
 25 compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.64-3.04 (6H,m), 3.15 (3H,d,J=7.1Hz),

3.41-3.53 (2H, m), 3.60-3.80 (4H, m), 4.35-4.43 (0.5H, m),
 4.44 (2H, s), 5.06-5.12 (0.5H, m), 5.25-5.35 (0.5H, m),
 5.86 (0.5H, br s), 7.02 (1H, s), 7.29 (1H, dd, J=8.8, 2.0 Hz),
 7.46 (1H, d, J=8.8 Hz), 7.75 (1H, s), 9.25 (2H, br s), 11.86 (1H, br
 5 s), 12.42 (1H, br s).

MS (FAB) m/z: 601 [(M+H)⁺, Cl³⁵], 603 [(M+H)⁺, Cl³⁷].

[Example B-118] N-[[1-[[6-(1-Acetoxyethoxy)carbonyl-
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-
 [(5-chloroindol-2-yl)sulfonyl]piperazin-2-
 10 yl]acetyl]methanesulfonamide

In ethanol (2 ml) was dissolved N-[[4-[(5-chloroindol-
 2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-
 c]pyridin-2-yl)carbonyl]piperazin-2-
 yl]acetyl]methanesulfonamide trifluoroacetate (97 mg),
 15 followed by the addition of triethylamine (0.63 ml) and 1-
 acetoxyethyl p-nitrophenyl carbonate (110 mg). The
 resulting mixture was stirred at room temperature for 4
 hours. The reaction mixture was concentrated under reduced
 pressure. Methylene chloride was added to the residue.

20 The resulting mixture was washed with water, dried over
 anhydrous sodium sulfate and distilled to remove the
 solvent. The residue was purified by chromatography on a
 silica gel column (methylene chloride : methanol = 50:1),
 whereby the title compound (50 mg) was obtained as a
 25 colorless foam.

¹H-NMR (DMSO-d₆) δ: 1.42 (3H, br s), 2.01 (3H, br s), 2.60-

2.90 (6H,m), 3.07-3.16 (3H,m), 3.64-3.80 (4H,m), 4.09-
 4.12 (0.5H,m), 4.35-4.41 (0.5H,m), 4.63-4.77 (2.5H,m), 5.05-
 5.11 (0.5H,m), 5.32-5.39 (0.5H,m), 5.89-5.96 (0.5H,m), 6.62-
 6.70 (1H,m), 7.02 (1H,s), 7.29 (1H,d,J=8.8Hz),
 5 7.46 (1H,d,J=8.8Hz), 7.75 (1H,s), 11.88 (1H,br s), 12.44 (1H,br
 s).

MS (FAB) m/z: 731 [(M+H)⁺, Cl³⁵], 733 [(M+H)⁺, Cl³⁷].

[Example B-119] 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-
 2-(N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-
 10 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
 hydrochloride

In the same manner as in Example B-62, the title
 compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.62 (3H,s), 2.66-4.49 (13.5H,m), 4.60-
 15 4.76 (1H,m), 5.05 (1/2H,br s), 5.50-5.62 (1/2H,m), 6.15-
 6.27 (1/2H,m), 7.57 (1H,d,J=8.8Hz), 8.07 (1H,d,J=8.8Hz),
 8.08 (1H,s), 8.17 (1/2H,br s), 8.23 (1/2H,br s), 8.37 (1H,s).
 MS (FAB) m/z: 554 [(M+H)⁺, Cl³⁵], 556 [(M+H)⁺, Cl³⁷].

[Example B-120] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-
 20 [(thiazolo[4,5-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-62, the title
 compound was obtained.

¹H-NMR (CDCl₃) δ: 3.27 (4H,br s), 3.90-4.03 (2H,m), 4.61-
 4.73 (2H,m), 7.58 (1H,dd,J=8.8,2.0Hz),
 25 7.79 (1H,dd,J=8.8,2.0Hz), 7.85-8.01 (4H,m), 8.34 (1H,s),

8.59 (1H, d, J=5.4 Hz), 9.35 (1H, d, J=1.0 Hz).

MS (FAB) m/z: 473 [(M+H)⁺, Cl³⁵], 475 [(M+H)⁺, Cl³⁷].

[Example B-121] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazolo[4,5-c]pyridine
5 N-oxide

In the same manner as in Example B-34, the title compound was obtained.

H-NMR (DMSO-d₆) δ: 3.15 (4H, br s), 3.80 (2H, br s), 4.32 (2H, br s), 7.70 (1H, dd, J=8.8, 2.0 Hz), 7.83 (1H, dd, J=8.8, 2.0 Hz),
10 8.15 (1H, d, J=8.8 Hz), 8.18 (1H, d, J=8.8 Hz), 8.22 (1H, s),
8.25 (1H, d, J=8.8 Hz), 8.30 (1H, d, J=2.0 Hz), 8.32 (1H, d, J=1.5 Hz),
8.51 (1H, s), 9.03 (1H, d, J=1.5 Hz).

MS (FAB) m/z: 489 [(M+H)⁺, Cl³⁵], 491 [(M+H)⁺, Cl³⁷].

[Example B-122] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5-methylthiazolo[4,5-c]pyridinium iodide
15

In the same manner as in Example B-33, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.10-3.25 (4H, m), 3.85 (2H, br s),
20 4.29 (2H, br s), 4.47 (3H, s), 7.71 (1H, dd, J=8.8, 2.0 Hz),
7.84 (1H, d, J=8.8 Hz), 8.17 (1H, d, J=8.8 Hz), 8.23 (1H, s),
8.26 (1H, d, J=8.8 Hz), 8.53 (1H, s), 8.86 (1H, d, J=6.8 Hz),
8.90 (1H, d, J=6.8 Hz), 10.03 (1H, s).

MS (FAB) m/z: 487, 489.

[Example B-123] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-

(N-methylcarbamoyl)-1-[(thiazolo[4,5-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

5 $^1\text{H-NMR}$ (DMSO- d_6 at 100°C) δ : 2.61 (3H, d, $J=4.9\text{Hz}$), 2.75-2.88 (1H, m), 2.98 (1H, dd, $J=12.7, 4.9\text{Hz}$), 3.20-3.80 (1H, m), 4.29 (1H, d, $J=2.7\text{Hz}$), 4.90-5.48 (1H, m), 7.61 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.79 (1H, br s), 7.81 (1H, dd, $J=8.8, 2.0\text{Hz}$), 8.04-8.10 (2H, m), 10 8.12 (1H, d, $J=5.4\text{Hz}$), 8.15 (1H, d, $J=8.8\text{Hz}$), 8.44 (1H, d, $J=1.0\text{Hz}$), 8.56 (1H, d, $J=5.4\text{Hz}$), 9.28 (1H, br s).

MS (FAB) m/z : 530 $[(M+H)^+, \text{Cl}^{35}]$, 532 $[(M+H)^+, \text{Cl}^{37}]$.

[Example B-124] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-(N-methylcarbamoyl)piperazin-1-yl]carbonyl]-5-methylthiazolo[4,5-c]pyridinium Iodide
15

In the same manner as in Example B-33, the title compound was obtained.

$^1\text{H-NMR}$ (DMSO- d_6 at 100°C) δ : 2.62 (3H, d, $J=4.4\text{Hz}$), 2.77-2.87 (1H, m), 2.94-3.03 (1H, m), 3.10-3.90 (2H, m), 20 4.31 (1H, d, $J=12.7\text{Hz}$), 4.50 (3H, s), 4.85-5.85 (2H, m), 7.64 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.80 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.82-7.90 (1H, m), 8.10 (1H, d, $J=8.8\text{Hz}$), 8.12 (1H, d, $J=2.0\text{Hz}$), 8.17 (1H, d, $J=8.8\text{Hz}$), 8.45 (1H, s), 8.86 (2H, d, $J=1.5\text{Hz}$), 9.93 (1H, br s).

25 MS (FAB) m/z : 544 (M^+ , Cl^{35}), 546 (M^+ , Cl^{37}).

[Example B-125] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(5-methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

5 The title compound was obtained in the same manner as in Referential Example 404 in which reduction by sodium borohydride had been employed.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.41-2.80 (5H,m), 3.12-3.78 (7H,m), 4.15-4.60 (2.5H,m), 4.97 (0.5H,br s), 5.35-5.48 (0.5H,m),
10 6.03 (0.5H,br s), 7.70 (1H,dd, $J=8.8, 2.0\text{Hz}$),
7.79 (1H,d, $J=8.8\text{Hz}$), 8.06-8.20 (2H,m), 8.22 (1H,s),
8.24 (1H,d, $J=8.8\text{Hz}$), 8.48 (1H,s), 11.20-11.63 (1H,m).

MS (FAB) m/z : 548 $[(M+H)^+, \text{Cl}^{35}]$, 550 $[(M+H)^+, \text{Cl}^{37}]$.

[Example B-126] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-
15 [(6-ethyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridin-2-yl)carbonyl]-2-(N-methylcarbamoyl)piperazine hydrochloride

In the same manner as in Referential Example 404, the title compound was obtained.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.28-1.40 (3H,m), 2.40-2.79 (5H,m), 3.10-
20 3.83 (10H,m), 4.15-4.60 (2.5H,m), 4.97 (0.5H,br s), 5.35-5.45 (0.5H,m), 6.05-6.12 (0.5H,m), 7.70 (1H,dd, $J=8.8, 2.0\text{Hz}$),
7.79 (1H,d, $J=8.8\text{Hz}$), 8.05-8.17 (2H,m), 8.22 (1H,s),
8.24 (1H,d, $J=8.8\text{Hz}$), 8.49 (1H,s), 11.01-11.20 (1H,m).

MS (FAB) m/z : 562 $[(M+H)^+, \text{Cl}^{35}]$, 564 $[(M+H)^+, \text{Cl}^{37}]$.

25 [Example B-127] tert-Butyl [2-[[4-[(6-chloronaphthalen-2-

yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-6-yl)acetate

In N,N-dimethylformamide (50 ml) was dissolved 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-

5 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
hydrochloride (240 mg), followed by the addition of
triethylamine (0.28 ml) and then tert-butyl bromoacetate
(0.14 ml). The resulting mixture was stirred overnight at
room temperature. After concentration of the reaction
10 mixture under reduced pressure, ethyl acetate was added to
the residue. The resulting mixture was washed with water,
dried over anhydrous sodium sulfate and distilled under
reduced pressure to remove the solvent. The residue was
purified by chromatography on a silica gel column (Φ 3.0 x
15 12.0 cm, hexane : ethyl acetate = 3:2), whereby the title
compound (207 mg) was obtained as a colorless foam.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (9H, s), 2.86-2.92 (2H, m),
3.00 (2H, t, $J=5.4\text{Hz}$), 3.18 (4H, br s), 3.35 (2H, s), 3.87 (2H, br
s), 3.90 (2H, s), 4.55 (2H, br s), 7.57 (1H, dd, $J=8.8, 2.0\text{Hz}$),
20 7.76 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.87-7.93 (3H, m), 8.31 (1H, s).

MS (FAB) m/z : 591 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 593 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Example B-128] Ethyl [2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-6-yl)acetate

25 In the same manner as in Example B-127, the title
compound was obtained.

¹H-NMR (CDCl₃) δ: 1.28 (3H, t, J=7.3 Hz), 2.85-2.95 (2H, m),
 2.97-3.07 (2H, m), 3.18 (4H, br s), 3.46 (2H, s), 3.87 (2H, br s),
 3.92 (2H, s), 4.20 (2H, q, J=7.3 Hz), 4.55 (2H, br s),
 7.57 (1H, d, J=8.8 Hz), 7.76 (1H, d, J=8.8 Hz), 7.82-7.95 (3H, m),
 8.31 (1H, s).

MS (FAB) m/z: 477 [(M+H)⁺, Cl³⁵], 479 [(M+H)⁺, Cl³⁷].

[Example B-129] [2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-6-yl)acetic acid
 trifluoroacetate

In methylene chloride (1 ml) was dissolved tert-butyl [2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-6-yl)acetate (200 mg), followed by the addition of
 trifluoroacetic acid (2 ml). The resulting mixture was
 stirred at room temperature for 2 hours. After
 concentration under reduced pressure, diethyl ether was
 added to the residue. The precipitate so formed was
 collected by filtration, whereby the title compound (193
 mg) was obtained as a colorless foam.

¹H-NMR (DMSO-d₆) δ: 2.96 (2H, br s), 3.08 (4H, br s), 3.27-
 3.96 (6H, m), 4.37 (4H, br s), 7.70 (1H, dd, J=8.8, 2.0 Hz),
 7.82 (1H, d, J=8.8 Hz), 8.20-8.28 (3H, m), 8.50 (1H, s).

MS (FAB) m/z: 535 [(M+H)⁺, Cl³⁵], 537 [(M+H)⁺, Cl³⁷].

[Example B-130] N-[[2-[[4-(6-Chloronaphthalen-2-

yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-6-
yl]acetyl]methanesulfonamide hydrochloride

In tetrahydrofuran (20 ml) was dissolved [2-[[4-[(6-
5 chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-6-yl]acetic acid
trifluoroacetate (110 mg), followed by the addition of
carbonyldiimidazole (60 mg). The resulting mixture was
heated under reflux for 1 hour. After the reaction was
10 cooled to room temperature, methanesulfonamide (34 mg) and
1,8-diazabicyclo[5.4.0]-7-undecene (0.05 ml) were added and
they were stirred for 30 minutes. The reaction mixture was
concentrated under reduced pressure. To the residue was
added methylene chloride, followed by washing with water,
15 0.2N hydrochloric acid and saturated aqueous NaCl solution,
each once. The organic layer thus extracted was dried over
anhydrous sodium sulfate and distilled under reduced
pressure to remove the solvent. The residue was purified
by chromatography on a silica gel column (methylene
20 chloride : methanol = 100:4), whereby colorless foam was
obtained. The resulting foam was suspended in a 1N aqueous
hydrochloric acid in ethanol solution (1 ml), followed by
concentration under reduced pressure and azeotropy with
water, whereby the title compound (44 mg) was obtained as
25 pale yellow foam.

¹H-NMR (DMSO-d₆) δ: 3.00 (2H, br s), 3.11 (4H, br s),

3.28 (3H, s), 3.32-4.06 (6H, m), 4.40 (4H, br s),
 7.70 (1H, dd, J=8.8, 2.0 Hz), 7.82 (1H, d, J=8.8 Hz),
 8.14 (1H, d, J=8.8 Hz), 8.22 (1H, s), 8.25 (1H, d, J=8.8 Hz),
 8.50 (1H, s).

5 MS (FAB) m/z: 612 [(M+H)⁺, Cl³⁵], 614 [(M+H)⁺, Cl³⁷].

[Example B-131] Ethyl [4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]carbonyl]piperazin-1-yl]acetate hydrochloride

10 In the same manner as in Example B-62, the title compound was obtained.

¹H-NMR (DMSO-d₆ at 100°C) δ: 1.26 (3H, t, J=7.2 Hz), 2.80-3.35 (13H, m) 3.44-3.89 (11H, m), 4.20 (2H, q, J=7.2 Hz),
 4.52 (2H, br s), 7.67 (1H, dd, J=8.8, 1.7 Hz),

15 7.81 (1H, d, J=8.8, 1.7 Hz), 8.11 (1H, d, J=8.8 Hz), 8.16 (1H, s),
 8.19 (1H, d, J=8.8 Hz), 8.47 (1H, s).

MS (FAB) m/z: 689 [(M+H)⁺, Cl³⁵], 691 [(M+H)⁺, Cl³⁷].

[Example B-132] [4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]carbonyl]piperazin-1-yl]acetic acid hydrochloride

20

In the same manner as in Example B-23, the title compound was obtained.

¹H-NMR (DMSO-d₆ at 100°C) δ: 2.84-2.93 (5H, m), 3.10-3.34 (7H, m), 3.45-3.61 (2H, m), 3.70-4.70 (12H, m),

25

7.67 (1H, dd, J=8.8, 2.0 Hz), 7.81 (1H, d, J=8.8, 1.7 Hz),
 8.11 (1H, d, J=8.8 Hz), 8.17 (1H, s), 8.20 (1H, d, J=8.8 Hz),
 8.48 (1H, s).

MS (FAB) m/z: 661 [(M+H)⁺, Cl³⁵], 663 [(M+H)⁺, Cl³⁷].

5 [Example B-133] N-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-
 1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 yl)carbonyl]piperazin-2-yl]carbonyl]methanesulfonamide
 hydrochloride

In tetrahydrofuran (30 ml) was dissolved 2-carbamoyl-
 10 4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-
 tetrahydrothiazolo[4,5-c]pyridin-2-yl)carbonyl]piperazine
 (300 mg), followed by the addition of a 0.5 mole toluene
 solution (1.12 ml) of potassium bis(trimethylsilyl)amide.
 The resulting mixture was stirred for 10 minutes under ice
 15 cooling. After the addition of methanesulfonyl chloride
 (0.04 ml), the resulting mixture was warmed up to room
 temperature and stirred for 1 hour. The reaction mixture
 was concentrated under reduced pressure. Methylene
 chloride was added to the residue and the resulting mixture
 20 was washed once with water and once with saturated aqueous
 NaCl solution. The organic layer thus extracted was dried
 over anhydrous sodium sulfate and distilled under reduced
 pressure to remove the solvent. The residue was purified
 by chromatography on a silica gel column (methylene
 25 chloride : methanol = 100:0 ~ 100:3), whereby colorless
 foam was obtained. The resulting foam was suspended in 1N

hydrochloric acid (1 ml). The resulting suspension was concentrated under reduced pressure, whereby the title compound (96 mg) was obtained as pale yellow foam.

¹H-NMR (DMSO-d₆) δ: 2.73-2.84 (1H,m), 2.90 (6H,s), 3.09-
 5 3.77 (8H,m), 3.99-4.27 (1H,m), 4.39-4.51 (1H,m), 4.69-
 4.79 (1H,m), 4.99 (1H,s), 7.64-7.73 (2H,m), 8.06-8.10 (1H,m),
 8.12-8.19 (1H,m), 8.44 (1H,s), 11.41 (1H,br s), 11.52 (1H,s).
 MS (FAB) m/z: 612 [(M+H)⁺, Cl³⁵], 614 [(M+H)⁺, Cl³⁷].

[Example B-134] 5-[2-[4-[(6-Chloronaphthalen-2-
 10 yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-
 2-yl)carbonyl]piperazin-2-yl]ethyl]tetrazole
 trifluoroacetate

In N,N-dimethylformamide (10 ml) were dissolved
 lithium 6-tert-butoxycarbonyl-4,5,6,7-
 15 tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate (329 mg),
 5-[2-[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-2-
 yl]ethyl]tetrazole trifluoroacetate (295 mg), 1-
 hydroxybenzotriazole monohydrate (9 mg) and 1-(3-
 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (114
 20 mg), followed by stirring overnight at room temperature.
 The reaction mixture was concentrated under reduced
 pressure. Methylene chloride was added to the residue and
 the resulting mixture was washed with water and saturated
 aqueous NaCl solution, each once. The organic layer was
 25 then dried over anhydrous sodium sulfate and distilled
 under reduced pressure to remove the solvent. The residue

was purified by chromatography on a silica gel column (methylene chloride : methanol = 25:2), whereby pale yellow foam (48 mg) was obtained. The resulting foam was dissolved in methylene chloride (1 ml), followed by the addition of trifluoroacetic acid (1 ml). After concentration under reduced pressure, the precipitate so formed was collected by filtration while being washed with diethyl ether, whereby the title compound (48 mg) was obtained as a colorless solid.

¹H-NMR (DMSO-d₆) δ: 1.12-1.40 (2H,m), 1.95-3.00 (7H,m), 3.42-3.47 (1H,m), 3.60-3.88 (2.5H,m), 4.10-4.15 (0.5H,br s), 4.38-4.45 (2H,m), 4.67-4.80 (1H,m), 5.25-5.31 (0.5H,m), 5.58-5.65 (0.5H,m), 7.70 (1H,d,J=8.8Hz), 7.82 (1H,d,J=8.8Hz), 8.14 (1H,d,J=8.8Hz), 8.18-8.26 (2H,m), 8.46-8.50 (1H,m).

MS (FAB) m/z: 573 [(M+H)⁺, Cl³⁵], 575 [(M+H)⁺, Cl³⁷].

[Example B-135] 5-[2-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]ethyl]tetrazole

In the same manner as in Example B-32, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.08-1.40 (2H,m), 1.90-3.84 (15.5H,m), 4.10 (0.5H,br s), 4.32-4.43 (0.5H,m), 4.72-4.80 (0.5H,m), 5.35-5.43 (0.5H,m), 5.69-5.80 (0.5H,m), 7.68 (1H,dd,J=8.8,2.0Hz).

MS (FAB) m/z: 587 [(M+H)⁺, Cl³⁵], 589 [(M+H)⁺, Cl³⁷].

[Example B-136] 5-[[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl)carbonyl]amino]methyl]tetrazole trifluoroacetate

5 In the same manner as in Example B-134, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.63-2.78 (1H,m), 2.85-2.93 (1H,m), 2.99-3.05 (1H,m), 3.28-3.79 (6H,m), 4.27-4.34 (1H,m), 4.40-4.70 (3.5H,m), 5.13-5.16 (0.5H,m), 5.48-5.56 (0.5H,m), 6.10-10 6.13 (0.5H,m), 7.70 (1H,d,J=8.8Hz), 7.79 (1H,d,J=8.8Hz), 8.08-8.26 (3H,m), 8.48 (1H,s), 8.89-9.00 (1H,m).

MS (FAB) m/z: 602 [(M+H)⁺, Cl³⁵], 604 [(M+H)⁺, Cl³⁷].

[Example B-137] 5-[[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl)carbonyl]amino]methyl]tetrazole

In the same manner as in Example B-32, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.36 (3H,s), 3.59 (1H,d,J=12.2Hz), 3.65-20 3.75 (1H,m), 4.16-4.56 (4.5H,m), 5.06 (0.5H,br s), 5.48-5.57 (0.5H,m), 6.20 (0.5H,br s), 7.67 (1H,dd,J=8.8,2.0Hz), 7.80 (1H,d,J=8.8Hz), 8.05-8.35 (4H,m), 8.49 (1H,s).

[Example B-138] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl)methyl]-4,5-dihydro-5-oxo-1,3,4-oxadiazole trifluoroacetate

In the same manner as in Example B-134, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.38-2.69 (2H,m), 2.92-3.11 (3H,m), 3.18-3.34 (1H,m), 3.40-3.88 (5H,m), 4.39-4.47 (2.5H,m),
 5 4.99 (0.5H,br s), 5.38-5.44 (0.5H,m), 5.72-5.88 (0.5H,br s),
 7.70 (1H,d,J=8.8Hz), 7.81 (1H,d,J=8.8Hz), 8.15 (1H,d,J=8.8Hz),
 8.22 (1H,s), 8.24 (1H,d,J=8.8Hz), 8.50 (1H,s), 9.23 (2H,br s),
 12.03 (0.5H,s), 12.08 (0.5H,s).

MS (FAB) m/z: 575 [(M+H)⁺, Cl³⁵], 577 [(M+H)⁺, Cl³⁷].

10 [Example B-139] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl)methyl]-4,5-dihydro-5-oxo-1,3,4-oxadiazole

15 In the same manner as in Example B-32, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.35 (3H,s), 2.37-2.82 (6H,m), 2.97-3.36 (2.5H,m), 3.45-3.88 (4.5H,m), 4.40-4.46 (0.5H,m),
 4.98 (0.5H,br s), 5.45-5.55 (0.5H,br s), 5.93 (0.5H,br s),
 7.70 (1H,dd,J=8.8,2.0Hz), 7.81 (1H,dd,J=8.8,2.0Hz),
 20 8.15 (1H,d,J=8.8Hz), 8.22 (1H,s), 8.24 (1H,d,J=8.8Hz),
 8.50 (1H,s), 11.91-12.10 (1H,m).

MS (FAB) m/z: 589 [(M+H)⁺, Cl³⁵], 591 [(M+H)⁺, Cl³⁷].

[Example B-140] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[[(morpholin-4-yl)carbonyl]methyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

25

hydrochloride

In the same manner as in Example B-1, the title compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.33-3.85 (19H,m), 4.35-4.50 (2.5H,m),
 5.01-5.08 (0.5H,m), 5.27-5.37 (0.5H,m), 5.68-5.78 (0.5H,m),
 7.03 (1H,s), 7.32 (1H,d,J=8.8Hz), 7.48 (1H,d,J=8.8Hz),
 7.77 (1H,s), 9.54 (2H,br s), 12.45 (1H,s).

MS (FAB) m/z : 593 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 595 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Example B-141] 1-[[6-(1-Acetoxyethoxy)carbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[[methyl(morpholin-4-yl)carbonyl]methyl]piperazine

In ethanol (6 ml) was dissolved 4-[(5-chloroindol-2-yl)sulfonyl]-2-[[methyl(morpholin-4-yl)carbonyl]methyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (200 mg), followed by the addition of diisopropylethylamine (83 μl) and 1-acetoxyethyl p-nitrophenyl carbonate (128 mg). The resulting mixture was stirred at room temperature for 5 hours. The solvent was distilled off under reduced pressure. Methylene chloride and an aqueous solution of sodium bicarbonate were added and the mixture was separated into layers. The organic layer was dried over anhydrous sodium sulfate and the filtrate was concentrated. The residue was purified by chromatography on a silica gel column (1-2% methanol - methylene chloride). The product

was dissolved in ethyl acetate, followed by crystallization from diethyl ether, whereby the title compound (100 mg) was obtained as colorless powder.

¹H-NMR (DMSO-d₆) δ: 1.43(3H,br s), 2.00-2.03(3H,m), 2.30-3.80(19H,m), 4.35-4.45(0.5H,m), 4.61-4.77(2H,m), 5.01-5.08(0.5H,m), 5.27-5.37(0.5H,m), 5.71-5.82(0.5H,m), 6.65-6.68(1H,m), 7.01(1H,s), 7.30(1H,d,J=8.8Hz), 7.47(1H,d,J=8.8Hz), 7.75(1H,s), 12.40(1H,s).

MS (FAB) m/z: 723 [(M+H)⁺, Cl³⁵], 725 [(M+H)⁺, Cl³⁷].

[Example B-142] 1-[[6-(tert-Butoxycarbonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)piperazine

In the same manner as in Example B-62, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.41(9H,s), 2.43-2.85(5H,m), 3.15-3.75(6H,m), 4.20-4.27(1H,m), 4.40-4.48(0.5H,m), 4.60-4.67(2H,m), 5.01(0.5H,s), 5.52-5.57(0.5H,m), 6.19(0.5H,br s), 6.99-7.01(1H,m), 7.30(1H,d,J=8.8Hz), 7.44-7.48(1H,m), 7.76(1H,s), 8.04-8.12(1H,m), 12.39(1H,s).

MS (FAB) m/z: 623 [(M+H)⁺, Cl³⁵], 625 [(M+H)⁺, Cl³⁷].

[Example B-143] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.43-2.75 (5H, m), 2.95 (1H, br s),
 3.02 (1H, br s), 3.15-3.25 (0.5H, m), 3.38-3.50 (2H, m), 3.50-
 3.62 (0.5H, m), 3.63-3.75 (1H, m), 4.20-4.27 (1H, m), 4.35-
 4.50 (2.5H, m), 5.00 (0.5H, br s), 5.42-5.53 (0.5H, m),
 5 6.15 (0.5H, br s), 7.01 (1H, s), 7.30 (1H, d, $J=8.8\text{Hz}$),
 7.47 (1H, d, $J=8.8\text{Hz}$), 7.77 (1H, s), 8.09-8.14 (1H, m), 9.43 (1H, br
 s), 12.42 (1H, s).

MS (FAB) m/z : 523 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 525 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Example B-144] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-
 10 hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 yl)carbonyl]-2-(N-methylcarbamoyl)piperazine

In methylene chloride (25 ml) were dissolved 4-[(5-
 chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-
 [(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 15 yl)carbonyl]piperazine (209 mg) and benzoyl peroxide (70%,
 138 mg) at room temperature, followed by heating under
 reflux for 9 hours. By the purification by chromatography
 on a silica gel column (4% methanol - methylene chloride),
 a crudely purified product of 1-[(6-benzoyloxy-4,5,6,7-
 20 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-
 chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)piperazine
 (190 mg) was obtained as a colorless glassy solid. The
 resulting solid was dissolved in a mixed solvent of
 tetrahydrofuran (20 ml) and methanol (20 ml), followed by
 25 the addition of a 1N aqueous solution (2.00 ml) of sodium
 hydroxide. The resulting mixture was stirred at room

temperature for 10 minutes. The solvent was distilled off and the residue was separated into layers by the addition of chloroform and water. The organic layer was dried over anhydrous sodium sulfate and the filtrate was concentrated.

5 The residue was purified by preparative thin-layer chromatography (4% methanol - methylene chloride) using silica gel, whereby the title compound (19 mg) was obtained as colorless powder.

¹H-NMR (CDCl₃) δ: 2.75-3.25(7H,m), 3.34(2H,br s), 3.58-
10 3.68(1H,m), 4.05-4.45(2H,br), 4.53-4.73(2H,m), 5.25(0.5H,br s), 5.50-5.75(2.5H,m), 6.11(0.5H,br s), 6.50(0.5H,s), 7.05(1H,br s), 7.25-7.32(1H,m), 7.35-7.45(1H,m), 7.64(1H,s), 10.73(1H,s).

HRMS (FAB) m/z: 539.0920 (M+H)⁺ (calcd for C₂₁H₂₄ClN₆O₅S₂,
15 539.0938).

[Example B-145] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

20 In the same manner as in Example B-94, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.40-2.85(7H,m), 2.89(3H,s), 3.00-
3.30(3H,br), 3.40-3.82(4H,m), 4.30-4.80(2.5H,br),
5.06(0.5H,br s), 5.26-5.40(0.5H,m), 5.81(0.5H,br s),
25 7.02(1H,s), 7.31(1H,d,J=8.6Hz), 7.48(1H,d,J=8.6Hz), 7.76(1H,s), 7.89-7.94(1H,m), 11.16(1H,br s), 12.44(1H,s).

MS (FAB) m/z: 551 [(M+H)⁺, Cl³⁵], 553 [(M+H)⁺, Cl³⁷].

[Example B-146] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(methoxycarbonyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

5 In the same manner as in Example B-62, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.49(3H,s), 2.50-2.90(7H,m), 2.95-3.06(1H,m), 3.10-3.25(0.5H,m), 3.35-3.50(0.5H,m), 3.50-3.70(5H,m), 3.70-3.95(2H,br), 4.60-4.64(0.5H,br),
10 5.22(0.5H,br s), 5.71-5.75(0.5H,m), 6.18(0.5H,br s), 6.96(1H,s), 7.31(1H,dd,J=8.8,1.7Hz), 7.36(1H,d,J=8.8Hz), 7.65(1H,d,J=1.7Hz), 9.15-9.20(1H,br).

MS (FAB) m/z: 552 [(M+H)⁺, Cl³⁵], 554 [(M+H)⁺, Cl³⁷].

[Example B-147] 2-(Carboxymethyl)-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
15

In the same manner as in Example B-77, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.38(3H,s), 2.40-3.81(13H,m), 4.36-4.41(0.5H,br), 5.01(0.5H,br s), 5.41-5.44(0.5H,m),
20 5.86(0.5H,br s), 7.03(1H,s), 7.31(1H,dd,J=8.8,1.7Hz), 7.47(1H,d,J=8.8Hz), 7.76(1H,d,J=1.7Hz), 12.42(1H,s).

MS (FAB) m/z: 538 [(M+H)⁺, Cl³⁵], 540 [(M+H)⁺, Cl³⁷].

[Example B-148] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[N-((1,3-dioxolan-2-yl)methyl)carbonyl]methyl]-1-[(6-methyl-
25

4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine

In the same manner as in Example B-79, the title compound was obtained.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 2.50 (3H, s), 2.51-3.10 (7H, m), 3.30-3.65 (3H, m), 3.68 (2H, s), 3.70-4.12 (6H, m), 4.46-4.57 (0.5H, m), 4.90-5.00 (1H, m), 5.10-5.20 (0.5H, m), 5.55-5.70 (0.5H, m), 5.87 (0.5H, s), 6.28 (0.5H, s), 6.52 (0.5H, s), 6.99 (1H, s), 7.28 (1H, d, $J=8.8\text{Hz}$), 7.37 (1H, d, $J=8.8\text{Hz}$), 7.64 (1H, s),
10 10.38 (0.5H, br s), 10.62 (0.5H, s).

MS (FAB) m/z : 623 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 625 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[Example B-149] 1-[[4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl)acetyl]piperidin-4-one
15 ethyleneketal

In the same manner as in Example B-79, the title compound was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.60 (4H, s), 2.49 (3H, s), 2.55-3.20 (7H, m), 3.20-3.35 (0.5H, m), 3.50-3.85 (8H, m), 4.00 (5H, br s), 4.12-
20 4.23 (0.5H, m), 4.55-4.67 (0.5H, m), 4.95-5.07 (0.5H, m), 5.45-5.60 (0.5H, m), 5.95-6.07 (0.5H, m), 7.00 (1H, s), 7.22-7.31 (1H, m), 7.37 (1H, d, $J=8.8\text{Hz}$), 7.64 (1H, s), 10.37 (0.5H, br s), 11.14 (0.5H, s).

MS (FAB) m/z : 663 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 665 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

25 [Example B-150] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N,N-

dimethylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-79, the title
5 compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.40-2.80(6H,m), 2.81-3.20(9H,m), 3.35-3.85(5H,m), 4.30-4.80(2.5H,br), 5.00(0.5H,br s), 5.26-5.40(0.5H,m), 5.75(0.5H,br s), 7.01(1H,s), 7.30(1H,d,J=8.6Hz), 7.47(1H,d,J=8.6Hz), 7.75(1H,s),
10 11.22(1H,br s), 12.42(1H,s).

MS (FAB) m/z: 565 [(M+H)⁺, Cl³⁵], 567 [(M+H)⁺, Cl³⁷].

[Example B-151] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[N-(2,2-diethoxyethyl)carbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

15 In the same manner as in Example B-79, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.15-1.27(6H,m), 2.50(3H,s), 2.55-3.10(8H,m), 3.30-3.90(10H,m), 4.00-4.15(1H,m), 4.45-4.60(1.5H,m), 5.12(0.5H,br s), 5.55-5.70(0.5H,m),
20 5.82(0.5H,br s), 6.19(0.5H,br s), 6.59(0.5H,br s), 7.01(1H,s), 7.22-7.31(1H,m), 7.36(1H,d,J=9.0Hz), 7.65(1H,s), 10.21(0.5H,br s), 10.72(0.5H,s).

MS (FAB) m/z: 653 [(M+H)⁺, Cl³⁵], 655 [(M+H)⁺, Cl³⁷].

[Example B-152] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

25

yl)carbonyl]-2-[[N-(
(tetrahydrofurfuryl)carbamoyl)methyl]piperazine
hydrochloride

In the same manner as in Example B-62, the title
5 compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.40-1.55 (1H,m), 1.65-1.90 (3H,m), 2.40-
2.89 (3H,br), 2.90 (3H,s), 3.00-3.40 (5H,m), 3.41-3.85 (9H,m),
4.25-4.70 (1.5H,m), 5.08 (0.5H,br s), 5.26-5.37 (0.5H,m),
5.83 (0.5H,br s), 7.03 (1H,s), 7.31 (1H,d,J=9.0Hz),
10 7.48 (1H,d,J=9.0Hz), 7.77 (1H,s), 8.07 (1H,br s), 11.00-
11.30 (1H,br), 12.43 (1H,s).

MS (FAB) m/z: 621 [(M+H)⁺, Cl³⁵], 623 [(M+H)⁺, Cl³⁷].

[Example B-153] 1-[[6-(tert-Butoxycarbonylaminosulfonyl)-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]-4-
15 [(5-chloroindol-2-yl)sulfonyl]-2-[[(morpholin-4-
yl)carbonyl)methyl]piperazine

To methylene chloride (3 ml) was added tert-butyl
alcohol (53 mg). While cooling to 0°C,
chlorosulfonylisocyanate (88 mg) was added to the resulting
20 mixture, followed by stirring for 10 minutes. To the
reaction mixture was added a solution of 4-[(5-chloroindol-
2-yl)sulfonyl]-2-[[(morpholin-4-yl)carbonyl)methyl]-1-
[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]]piperazine (300 mg) and triethylamine (475 mg)
25 in methylene chloride (3 ml). After stirring at room
temperature for 1 hour, water was added to the reaction

mixture and the resulting mixture was extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by column chromatography (methanol : methylene chloride = 1:19) using as a carrier silica gel, whereby the title compound (311 mg) was obtained. A portion of the compound was purified further by preparative thin-layer chromatography (methanol : methylene chloride = 1:9) using silica gel, followed by the addition of ether. The instrumental data on the resulting pale yellow solid was as follows:

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.23, 1.24 (total 9H, each s), 2.33-3.75 (19H, m), 4.37-5.86 (4H, m), 7.03 (1H, s), 7.31 (1H, d, $J=8.8\text{Hz}$), 7.47 (1H, d, $J=8.8\text{Hz}$), 7.76 (1H, s), 11.21 (1H, s), 12.42 (1H, s).

MS (FAB) m/z : 772 ($\text{M}+\text{H}$) $^+$.

[Example B-154] 1-[[6-(Aminosulfonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[[methyl]piperazine

In methylene chloride (3 ml) was dissolved 1-[[6-(tert-butoxycarbonylaminosulfonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[[methyl]piperazine (275 mg), followed by the

addition of trifluoroacetic acid (3 ml). The resulting mixture was stirred at room temperature for 30 minutes. The solvent was distilled off under reduced pressure. A saturated solution of hydrochloride in ethanol (3 ml) was added and the resulting mixture was stirred at room temperature for 1.5 hours. The residue obtained by distilling off the solvent under reduced pressure was added with methylene chloride and water to separate into layers. The water layer was extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by preparative thin-layer chromatography (methanol : methylene chloride = 1:9) using silica gel. The solid thus obtained was dissolved in a small amount of methylene chloride, followed by solidification by the addition of diethyl ether, whereby the title compound (50 mg) was obtained as a pale yellow solid.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.33-3.75 (19H,m), 4.35-5.84 (4H,m), 7.01-7.02 (3H,m), 7.31 (1H,d,J=8.8Hz), 7.48 (1H,d,J=9.0Hz), 7.76 (1H,s), 12.41 (1H,s).

MS (FAB) m/z : 672 ($\text{M}+\text{H}$) $^+$.

[Example B-155] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[(morpholin-4-yl)carbonyl]methyl]-1-[6-[phenylsulfonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine

In the same manner as in Example B-95, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.33-3.74 (19H,m), 4.34-5.71 (4H,m),
7.02 (1H,s), 7.31 (1H,d,J=8.6Hz), 7.47 (1H,d,J=9.0Hz), 7.57-
5 7.61 (2H,m), 7.65-7.67 (1H,m), 7.76 (1H,s),
7.80 (2H,d,J=7.8Hz), 12.40 (1H,s).

HRMS (FAB) m/z: 733.1333 (M+H)⁺ (calcd for C₃₁H₃₃ClN₆O₇S₃,
733.1340).

[Example B-156] 5-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-
10 c]pyridin-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-
2-(N-methylcarbamoyl)-1-[[6-(tert-butoxycarbonyl)piperazine

In diethyl ether (8 ml) dried by a molecular sieve was
dissolved 6-(tert-butoxycarbonyl)-5-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridine (203 mg). After the
15 container employed was purged with argon, the temperature
was cooled to -78°C. To the resulting solution, n-butyl
lithium (a 1.66 mole n-hexane solution, 506 μl) was added
dropwise, followed by stirring at the same temperature for
1.5 hours. While a carbon dioxide gas was blown into the
20 reaction mixture, the mixture was stirred at the same
temperature for 1 hour. After warming up to room
temperature, the solvent was distilled off under reduced
pressure, whereby crude lithium 6-(tert-butoxycarbonyl)-5-
methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-
25 carboxylate was obtained. This product was provided for
the subsequent reaction without purification. In N,N-

dimethylformamide (4 ml) was dissolved 3-(N-methylcarbamoyl)-1-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]piperazine (248 mg), followed by the addition of the crude lithium 6-(tert-butoxycarbonyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate (ca. 550 μ mol), which had been obtained above, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (144 mg) and 1-hydroxybenzotriazole (34 mg). The resulting mixture was stirred overnight at room temperature. Methylene chloride was added to the reaction mixture. The resulting mixture was washed with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by flash column chromatography (hexane : ethyl acetate = 2:1) using as a carrier silica gel, whereby the title compound (121 mg) was obtained as a white solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.12-1.17 (3H, m), 1.49 (9H, s), 2.62-3.23 (7H, m), 3.63 (1H, d, $J=12.3\text{Hz}$), 4.22 (1H, d, $J=17.9\text{Hz}$), 4.55-4.74 (2H, m), 4.83-4.89 (1H, m), 5.09-5.16 (1H, m), 5.25-6.49 (2H, m), 7.06 (1H, s), 7.27-7.30 (2H, m), 7.38-7.42 (1H, m), 7.64 (1H, s), 10.62-10.67 (1H, m).

[Example B-157] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.39-1.40 (3H,m), 2.32-3.68 (10H,m),
4.21-5.00 (4H,m), 5.44-6.15 (1H,m), 7.01 (1H,s),
5 7.31 (1H,dd, $J=8.5, 2.0\text{Hz}$), 7.48 (1H,d, $J=8.5\text{Hz}$), 7.77 (1H,s),
8.11-8.14 (1H,m), 9.38-9.75 (2H,m), 12.42 (1H,s).
 HRMS (FAB) m/z : 537.1140 ($\text{M}+\text{H}$) $^+$ (calcd for $\text{C}_{22}\text{H}_{26}\text{N}_6\text{O}_4\text{ClS}_2$,
537.1145).

[Example B-158] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(5,6-
10 dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]-2-(N-methylcarbamoyl)piperazine hydrochloride

In a saturated solution of hydrochloride in ethanol (2
ml) was dissolved 1-[[6-(tert-butoxycarbonyl)-5-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]-4-
15 [(5-chloroindol-2-yl)sulfonyl]-2-(N-
methylcarbamoyl)piperazine (40 mg), followed by stirring at
room temperature for 1 hour. Diethyl ether was added to
the reaction mixture. The precipitate so formed was
collected by filtration and washed with diethyl ether.
20 Methylene chloride (7 ml) and triethylamine (81 μl) were
added, followed by the addition of acetic acid (34 μl). To
the resulting mixture were added a 30% aqueous solution (21
 μl) of formaldehyde and sodium triacetoxyborohydride (64
mg), followed by stirring at room temperature for 30
25 minutes. The solvent was distilled off under reduced
pressure. Methylene chloride was added and the resulting

mixture was washed with water and saturated aqueous NaCl solution. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in a 1N ethanol hydrochloride solution. After stirring at room temperature for 5 minutes, the solvent was distilled off under reduced pressure. The precipitate so formed was collected by filtration and washed with diethyl ether, whereby the title compound (68 mg) was obtained as a white solid.

^1H -NMR (DMSO- d_6) δ : 1.32-1.40 (3H,m), 2.33-3.94 (13H,m), 4.23-4.26 (1H,m), 4.44-5.01 (3H,m), 5.50-6.16 (1H,m), 7.02 (1H,s), 7.31 (1H,dd,J=8.8,2.0Hz), 7.48 (1H,d,J=8.8Hz), 7.77 (1H,s), 8.10-8.16 (1H,m), 11.15-11.54 (1H,m), 12.43 (1H,s).

[Example B-159] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine trifluoroacetate

To a solution of 6-(tert-butoxycarbonyl)-2-methoxycarbonyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine (120 mg) in tetrahydrofuran (4.0 ml) were added water (1.0 ml) and lithium hydroxide (18.0 mg) at room temperature. After stirring for 10 minutes, the solvent was distilled off under reduced pressure. To a solution of the residue in N,N-dimethylformamide were added 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-(N-methylcarbamoyl)piperazine

hydrochloride (190 mg), 1-hydroxybenzotriazole monohydrate (11.5 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (90.0 mg) at room temperature. After stirring for 4 hours, methylene chloride (30 ml) and water (250 ml) were added to the reaction mixture to separate it into layers. The water layer was extracted with methylene chloride (20 ml). The organic layers were combined, washed with a saturated aqueous solution (50 ml) of sodium bicarbonate, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 25 g, methylene chloride : acetone = 5:1 → 3:1), whereby a colorless transparent oil was obtained. To a solution of the resulting substance in methylene chloride (4.0 ml) was added trifluoroacetic acid (4.0 ml) at room temperature and the resulting mixture was stirred for 1 hour. The reaction mixture was concentrated under reduced pressure. The residue was reprecipitated from a methylene chloride - methanol - diethyl ether system, whereby the title compound (165 mg) was obtained as a pale brown solid.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.30-2.70 (2H,m), 2.58 (3H,d,J=3.9Hz), 2.77 (2H,br d,J=16.1Hz), 3.05-3.60 (3H,m), 3.71 (1H,br d,J=11.2Hz), 4.29 (1H,br d,J=11.7Hz), 4.35-4.50 (2H + 1/2 of 1H,m), 4.96 (1/2 of 1H,br s), 5.05 (1/2 of 1H,br d,J=13.2Hz), 5.78 (1/2 of 1H,br s), 7.71 (1H,d,J=8.3Hz), 7.73-7.83 (1H,m), 8.00-8.20 (1H,m), 8.15 (1H,d,J=8.3Hz), 8.24 (1H,s),

8.25 (1H, d, J=8.3 Hz), 8.48 (1/2 of 1H, s), 8.49 (1/2 of 1H, s),
9.34 (2H, br s).

MS (FAB) m/z: 518 (M+H)⁺.

[Example B-160] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-
5 (N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-
tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-32, the title
compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.48 (3H, s), 2.52-2.80 (6H, m), 2.80-
10 3.00 (3H, m), 3.10 (1/2 of 1H, t, J=11.2 Hz), 3.49 (1/2 of
1H, t, J=11.2 Hz), 3.54 (2H, s), 3.78 (1/2 of 1H, br d, J=10.3 Hz),
3.86 (1/2 of 1H, br d, J=11.2 Hz), 4.45 (1H, t, J=11.4 Hz),
4.63 (1/2 of 1H, br d, J=12.7 Hz), 5.24 (1/2 of 1H, s), 5.38 (1/2
of 1H, br d, J=12.7 Hz), 6.12 (1/2 of 1H, br s), 6.16 (1/2 of
15 1H, s), 6.40 (1/2 of 1H, br s), 7.58 (1H, d, J=7.8 Hz),
7.80 (1H, d, J=7.8 Hz), 7.86-7.96 (3H, m), 8.34 (1H, s).

MS (FAB) m/z: 532 (M+H)⁺.

[Example B-161] 1-[[6-(tert-Butoxycarbonyl)-4,5,6,7-
tetrahydrooxazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-
20 chloroindol-2-yl)sulfonyl]piperazine

In the same manner as in Example B-62, the title
compound was obtained.

¹H-NMR (CDCl₃) δ: 1.46 (9H, s), 2.64 (2H, br s), 3.22 (4H, br s),
3.71 (2H, br s), 3.90 (2H, br s), 4.42 (2H, br s), 4.53 (2H, br s),
25 6.97 (1H, d, J=2.0 Hz), 7.33 (1H, dd, J=8.8, 2.0 Hz),

7.37 (1H, d, J=8.8Hz), 7.67 (1H, s), 8.71 (1H, br s).

[Example B-162] 1-[[6-(tert-Butoxycarbonyl)-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[[methylpiperazine

5 yl)carbonyl]methyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.47 (9H, s), 2.50-2.70 (2H, m), 2.70-3.20 (2H + 1/2 of 1H, m), 3.38 (1/2 of 1H, t, J=11.2Hz), 3.50-3.95 (11H + 1/2 of 1H, m), 3.99 (1/2 of 1H, br d, J=12.7Hz), 4.40-4.60 (1/2 of 1H, br), 4.53 (2H, s), 4.64 (1/2 of 1H, br d, J=13.7Hz), 5.02 (1/2 of 1H, br s), 5.24 (1/2 of 1H, br s), 5.79 (1/2 of 1H, br s), 7.00 (1H, s), 7.20-7.35 (1H, m), 7.38 (1H, d, J=8.8Hz), 7.65 (1/2 of 1H, s), 7.67 (1/2 of 1H, s), 9.89 (1/2 of 1H, br s), 10.60-11.00 (1/2 of 1H, br).

[Example B-163] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

To a solution of 1-[[6-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine (100 mg) in methylene chloride (3.0 ml) was added trifluoroacetic acid (3.0 ml) at room temperature, followed by stirring for 15 minutes. The reaction mixture was concentrated under reduced pressure. To the residue were added methylene chloride (4.0 ml), triethylamine (50.0 μl), acetic acid (21.0 μl),

formalin (23.5 μ l) and sodium triacetoxyborohydride (58.0 mg) at room temperature. After stirring for 1 hour, methylene chloride (20 ml) and a saturated aqueous solution (50 ml) of sodium bicarbonate were added to the reaction mixture to separate it into layers. The water layer was extracted with methylene chloride (20 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by preparative thin-layer chromatography (chloroform : methanol = 10:1) using silica gel, whereby the free form (82.6 mg) of the title compound was obtained as a colorless solid. To the resulting compound were added a 1N aqueous solution of hydrochloric acid, tetrahydrofuran and methanol, followed by concentration under reduced pressure, whereby the title compound was obtained as a colorless solid.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.90(4H,s), 3.11(3H,br s), 3.25-3.75(2H,br), 3.35(2H,s), 3.75(2H,br s), 4.16(2H,br s), 4.20-4.75(2H,br), 7.04(1H,s), 7.32(1H,dd,J=8.8,1.0Hz), 7.50(1H,d,J=8.8Hz), 7.78(1H,d,J=1.0Hz), 11.51(1H,br s), 12.46(1H,s).

MS (FAB) m/z : 464 ($\text{M}+\text{H}$) $^+$.

[Example B-164] 4-(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[methyl(4-morpholin-4-yl)carbonyl]methyl]piperazine hydrochloride

In the same manner as in Example B-163, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.30-2.75 (2H,m), 2.75-3.20 (2H,m),
2.90 (3H,s), 3.20-3.90 (15H,m), 4.30-4.45 (1H + 1/2 of 1H,m),
5 4.55-4.70 (1H,m), 4.89 (1/2 of 1H,br s), 5.05 (1/2 of 1H,br
s), 5.47 (1/2 of 1H,br s), 7.04 (1H,s), 7.29-7.35 (1H,m),
7.50 (1H,dd,J=8.8,2.9Hz), 7.76-7.80 (1H,m), 11.45-
11.95 (1H,br), 12.49 (1H,br s).

MS (FAB) m/z: 591 (M+H)⁺.

10 [Example B-165] 1-[[6-(tert-Butoxycarbonyl)-4,5,6,7-
tetrahydrooxazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(6-
chlorobenzo[b]thien-2-yl)sulfonyl]piperazine

To a solution of lithium 6-(tert-butoxycarbonyl)-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate
15 (70.0 mg) in N,N-dimethylformamide (4.0 ml) were added 1-
[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazine
hydrochloride (90.0 mg), 1-hydroxybenzotriazole monohydrate
(7.0 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
(64.0 mg) at room temperature. After stirring for 2 days,
20 ethyl acetate (30 ml) and water (500 ml) were added to the
reaction mixture to separate it into layers. The water
layer was extracted with ethyl acetate (30 ml). The
organic layers were combined, washed with a saturated
aqueous solution of sodium bicarbonate (100 ml), dried over
25 anhydrous sodium sulfate and distilled under reduced
pressure to remove the solvent. The residue was purified

by preparative thin-layer chromatography (hexane : ethyl acetate = 1:1) using silica gel, whereby the title compound (37.9 mg) was obtained as a colorless transparent glassy substance.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.47(9H,s), 2.65(2H,s),
3.27(4H,t,J=5.0Hz), 3.70(2H,s), 3.91(2H,s), 4.42(2H,s),
4.53(2H,s), 7.45(1H,dd,J=8.8,1.5Hz), 7.77(1H,s),
7.81(1H,d,J=8.8Hz), 7.86(1H,d,J=1.5Hz).
MS (FAB) m/z: 567 (M+H) $^+$.

10 [Example B-166] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-
4-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-163, the title compound was obtained.

15 $^1\text{H-NMR}$ (DMSO-d_6) δ : 2.90(3H,s), 2.94(1H,br s), 3.10-
3.25(4H,m), 3.49(2H,s), 3.64(1H,br s), 3.79(2H,s),
4.21(2H,s), 4.39(1H,br s), 4.60(1H,br s),
7.58(1H,dd,J=8.8,2.0Hz), 8.07(1H,d,J=8.8Hz), 8.10(1H,s),
8.34(1H,d,J=2.0Hz), 11.70(1H,br s).

20 MS (FAB) m/z: 481 (M+H) $^+$.

[Example B-167] 1-[(6-Methyl-4,5,6,7-
tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(1-
phenylsulfonyl-5-trimethylsilylethynylindol-2-
yl)sulfonyl]piperazine

25 In the same manner as in Example B-103, the title

compound was obtained.

¹H-NMR (CDCl₃) δ: 0.25 (9H, s), 2.51 (3H, s),
2.69 (2H, t, J=5.4Hz), 2.78 (2H, t, J=5.4Hz), 3.52 (2H, br s),
3.55 (2H, br s), 3.59 (2H, s), 3.89 (2H, br s), 4.41 (2H, br s),
5 7.42 (2H, t, J=7.6Hz), 7.47 (1H, s), 7.55 (1H, t, J=7.6Hz),
7.59 (1H, dd, J=8.8, 1.7Hz), 7.69 (1H, d, J=1.7Hz),
8.00 (2H, d, J=7.6Hz), 8.22 (1H, d, J=8.8Hz).

[Example B-168] 1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
10

In the same manner as in Example B-104, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.48 (3H, s), 2.66 (2H, t, J=5.4Hz),
2.75 (2H, t, J=5.4Hz), 3.04 (1H, s), 3.21 (4H, t, J=4.4Hz),
15 3.54 (2H, s), 3.89 (2H, br s), 4.43 (2H, br s), 7.00 (1H, s),
7.37 (1H, d, J=8.6Hz), 7.47 (1H, dd, J=8.6, 1.5Hz), 7.86 (1H, br s),
8.85 (1H, br s).

MS (FAB/glycerol) m/z: 454 (M+H)⁺.

[Example B-169] 1-[[6-(tert-Butoxycarbonyl)-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-ethylpiperazine
20

In the same manner as in Example B-165, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 0.90 (1/2 of 3H, t, J=7.1Hz), 0.96 (1/2 of
25 3H, t, J=7.1Hz), 1.47 (9H, s), 1.78-2.03 (2H, m), 2.45-

2.73(4H,m), 3.18(1/2 of 1H,t,J=11.5Hz), 3.51(1/2 of
 1H,t,J=11.5Hz), 3.60-3.92(4H,m), 4.52(2H,s), 4.62(1/2 of
 1H,d,J=13.0Hz), 4.79(1/2 of 1H,br s), 5.20(1/2 of 1H,br s),
 5.40(1/2 of 1H,br s), 6.94(1H,d,J=1.5Hz),
 5 7.31(1H,dd,J=8.8,2.0Hz), 7.37(1H,d,J=8.8Hz),
 7.66(1H,d,J=2.0Hz), 8.87(1H,br s).

MS (FAB) m/z: 578 (M+H)⁺.

[Example B-170] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-ethyl-
 1-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-
 10 yl]carbonyl]piperazine trifluoroacetate

To a solution of 1-[[6-(tert-butoxycarbonyl)-4,5,6,7-
 tetrahydrooxazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-
 chloroindol-2-yl)sulfonyl]-2-ethylpiperazine (320 mg) in
 methylene chloride (5.0 ml) was added trifluoroacetic acid
 15 (5.0 ml) at room temperature, followed by stirring for 10
 minutes. The reaction mixture was concentrated under
 reduced pressure, whereby the title compound (423 mg) was
 obtained as a pale brown solid.

¹H-NMR (DMSO-d₆) δ: 0.78(1/2 of 3H,t,J=6.9Hz), 0.83(1/2 of
 20 3H,t,J=6.9Hz), 1.47(9H,s), 1.65-1.95(2H,m), 2.30-
 2.70(2H,m), 2.80(2H,s), 3.13(1/2 of 1H,t,J=12.7Hz), 3.37-
 4.00(2H + 1/2 of 1H,m), 3.42(2H,s), 4.30-4.47(2H + 1/2 of
 1H,m), 4.60(1/2 of 1H,br s), 4.73(1/2 of 1H,d,J=14.0Hz),
 4.91(1/2 of 1H,br s), 8.01(1H,s), 7.30(1H,d,J=8.8Hz),
 25 7.47(1H,d,J=8.8Hz), 7.76(1H,s), 9.36(2H,br s), 12.42(1H,s).

MS (FAB) m/z: 478 (M+H)⁺.

[Example B-171] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-ethyl-
1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-32, the title
5 compound was obtained.

¹H-NMR (DMSO-d₆) δ: 0.73-0.83(3H,m), 1.60-1.92(2H,m), 2.30-
2.70(2H,m), 2.75-3.03(2H,m), 2.89(3H,s), 3.03-3.53(2H + 1/2
of 1H,m), 3.53-3.80(2H + 1/2 of 1H,m), 4.20-4.45(1H + 1/2
of 1H,br), 4.60(1H + 1/2 of 1H,br s), 4.76(1/2 of
10 1H,d,J=13.0Hz), 4.92(1/2 of 1H,br s), 7.00(1H,s),
7.30(1H,dd,J=8.8,2.0Hz), 7.47(1H,d,J=8.8Hz),
7.75(1H,d,J=2.0Hz), 11.57(1H,br s), 12.43(1H,s).

MS (FAB) m/z: 492 (M+H)⁺.

[Example B-172] 1-[[6-(tert-Butoxycarbonyl)-5,6,7,8-
15 tetrahydropyrido[4,3-d]pyrimidin-2-yl]carbonyl]-4-[(5-
chloroindol-2-yl)sulfonyl]piperazine

In the same manner as in Example B-159, the title
compound was obtained.

¹H-NMR (CDCl₃) δ: 1.49(9H,s), 2.96(2H,t,J=5.9Hz),
20 3.14(2H,t,J=5.0Hz), 3.27(2H,t,J=5.1Hz), 3.53(2H,t,J=5.0Hz),
3.75(2H,t,J=5.9Hz), 3.93(2H,t,J=5.1Hz), 4.62(2H,s),
6.96(1H,s), 7.35(1H,dd,J=8.5,1.7Hz), 7.38(1H,d,J=8.5Hz),
7.69(1H,d,J=1.7Hz), 8.48(1H,s), 8.77(1H,br s).

MS (FAB) m/z: 561 (M+H)⁺.

[Example B-173] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-

[(5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl)carbonyl]piperazine trifluoroacetate

In the same manner as in Example B-170, the title compound was obtained.

5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 2.96(2H,t,J=4.5Hz), 3.03(2H,t,J=6.0Hz),
 3.11(2H,t,J=4.5Hz), 3.29(2H,t,J=4.5Hz), 3.49(2H,br s),
 3.75(2H,t,J=4.5Hz), 4.36(2H,s), 7.03(1H,s),
 7.32(1H,dd,J=8.8,1.7Hz), 7.49(1H,d,J=8.8Hz),
 7.78(1H,d,J=1.7Hz), 8.70(1H,s), 9.25(2H,br s), 12.46(1H,s).
 10 MS (FAB) m/z : 461 ($\text{M}+\text{H}$) $^+$.

[Example B-174] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl)carbonyl]piperazine hydrochloride

15 In the same manner as in Example B-32, the title compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.92(3H,s), 2.98(2H,br s), 3.06(1H,br s),
 3.13(2H,t,J=5.0Hz), 3.28(1H,br s), 3.32(2H,t,J=5.0Hz),
 3.46(1H,br s), 3.70(1H,br s), 3.77(2H,br s), 4.34(1H,br d,J=15.4Hz),
 4.57(1H,br d,J=15.4Hz), 7.04(1H,d,J=1.6Hz),
 20 7.34(1H,dd,J=8.8,2.0Hz), 7.62(1H,d,J=8.8Hz),
 7.79(1H,d,J=2.0Hz), 8.71(1H,s), 11.67(1H,br s),
 12.50(1H,d,J=1.6Hz).
 MS (FAB) m/z : 475 ($\text{M}+\text{H}$) $^+$.

[Example B-175] 1-[[6-(tert-Butoxycarbonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl]carbonyl]-4-[(5-

25

chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)piperazine

In the same manner as in Example B-159, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.49(1/2 of 9H,s), 1.50(1/2 of 9H,s),
 5 2.60-2.72(1/2 of 1H,m), 2.85-3.12(6H,m), 3.12-3.30(1H,m),
 3.45-3.70(1H,m), 3.70-3.90(2H + 1/2 of 1H,m), 4.32(1/2 of
 1H,br s), 4.60-4.75(1/2 of 1H + 2H,m), 4.81(1/2 of
 1H,d,J=12.9Hz), 5.31-5.35(1/2 of 1H,m), 6.68(1/2 of 1H,br
 s), 7.04(1/2 of 1H,s), 7.07(1/2 of 1H,s), 7.20-7.35(1H,m),
 10 7.39(1/2 of 1H,d,J=8.8Hz), 7.40(1/2 of 1H,d,J=8.3Hz),
 7.62(1/2 of 1H,s), 7.66(1/2 of 1H,s), 7.87(1/2 of 1H,br s),
 10.47(1/2 of 1H,br s), 10.70(1/2 of 1H,br s).

MS (FAB) m/z: 618 (M+H)⁺.

[Example B-176] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-
 15 methylcarbamoyl)-1-[(5,6,7,8-tetrahydropyrido[4,3-
 d]pyrimidin-2-yl)carbonyl]piperazine trifluoroacetate

In the same manner as in Example B-170, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.30-2.58(2H,m), 2.60(1/2 of
 20 3H,d,J=4.4Hz), 2.64(1/2 of 3H,d,J=4.2Hz), 2.65-2.75(1H,m),
 3.00(1/2 of 2H,t,J=5.4Hz), 3.06(1/2 of 2H,t,J=6.2Hz),
 3.29(1/2 of 1H,br t,J=11.0Hz), 3.39(1/2 of 1H,br
 d,J=13.5Hz), 3.50(2H,br s), 3.53-3.80(1/2 of 1H + 1H,m),
 4.10-4.30(1/2 of 1H,m), 4.35(1/2 of 2H,s), 4.38(1/2 of
 25 2H,s), 4.50(1/2 of 1H,br d,J=13.5Hz), 5.05(1/2 of 1H,br s),
 7.00(1/2 of 1H,s), 7.01(1/2 of 1H,s), 7.28-7.38(1H,m),

7.48 (1/2 of 1H, d, J=8.8Hz), 7.49 (1/2 of 1H, d, J=8.8Hz),
 7.77 (1/2 of 1H, d, J=1.7Hz), 7.78 (1/2 of 1H, d, J=1.7Hz), 7.90-
 8.03 (1/2 of 1H, m), 8.07-8.17 (1/2 of 1H, m), 8.69 (1/2 of
 1H, s), 8.73 (1/2 of 1H, s), 9.24 (2H, br s), 12.43 (1H, s).

5 MS (FAB) m/z: 518 (M+H)⁺.

[Example B-177] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl)carbonyl]piperazine hydrochloride

10 In the same manner as in Example B-32, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.30-2.55 (2H, m), 2.61 (1/2 of
 3H, d, J=3.5Hz), 2.65 (1/2 of 3H, d, J=4.2Hz), 2.68-2.77 (1H, m),
 2.93 (3H, br s), 2.97-3.18 (1H, m), 3.20-3.80 (6H, m), 4.04-
 4.65 (3H, m), 5.07 (1/2 of 1H, br s), 7.00 (1/2 of
 15 1H, d, J=1.5Hz), 7.02 (1/2 of 1H, d, J=1.7Hz), 7.30-7.37 (1H, m),
 7.50 (1/2 of 1H, d, J=8.8Hz), 7.51 (1/2 of 1H, d, J=8.8Hz),
 7.78 (1/2 of 1H, d, J=1.7Hz), 7.80 (1/2 of 1H, d, J=2.0Hz),
 8.05 (1/2 of 1H, br s), 8.15 (1/2 of 1H, br d, J=4.2Hz),
 8.70 (1/2 of 1H, s), 8.74 (1/2 of 1H, s), 11.68 (1H, br s),
 20 12.48 (1H, s).

MS (FAB) m/z: 532 (M+H)⁺.

[Example B-178] 4-(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(piperidin-1-yl)ethyl]piperazine
 25 hydrochloride

In the same manner as in Example B-62, the title

compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.16-3.79 (26H,m), 4.37-4.45 (1H,m),
4.68-4.75 (2H,m), 5.40-5.47 (1H,m), 7.02 (1H,d,J=5.1Hz),
7.32 (1H,dd,J=2.2,8.8Hz), 7.49 (1H,d,J=8.8Hz), 7.77 (1H,s).

5 MS (FAB) m/z: 591 [(M+H)⁺, Cl³⁵], 593 [(M+H)⁺, Cl³⁷].

[Example B-179] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-[N-(2-methoxyethyl)amino]ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

10 In the same manner as in Example B-62, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.33-4.77 (21H,m), 3.29 (3H,s),
3.34 (3H,s), 5.39-5.43 (1H,m), 7.01 (1H,d,J=4.4Hz),
7.30 (1H,dd,J=7.8,2.0Hz), 7.49 (1H,d,J=8.8Hz), 7.76 (1H,s).

15 MS (FAB) m/z: 581 [(M+H)⁺, Cl³⁵], 583 [(M+H)⁺, Cl³⁷].

[Example B-180] 1-[[6-(tert-Butoxycarbonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[2-(piperidin-1-yl)ethyl]piperazine

20 In the same manner as in Example B-62, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.48 (9H,s), 1.16-3.79 (23H,m), 4.45-
4.59 (1H,m), 4.65-4.75 (2H,m), 6.70-6.80 (1H,m), 6.96 (1H,s),
7.28-7.31 (1H,m), 7.64 (1H,d,J=1.7Hz), 8.02 (1H,s).

25 MS (FAB) m/z: 677 (M+H)⁺.

[Example B-181] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methylsulfonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(piperidin-1-yl)ethyl]piperazine

In the same manner as in Example B-95, the title
5 compound was obtained.

¹H-NMR (CDCl₃) δ: 1.54-3.83(23H,m), 2.89(3H,s), 4.59(2H,s),
4.55-4.84(1H,m), 5.61-5.84(1H,m), 7.00(1H,d,J=15.0Hz),
7.27-7.29(1H,m), 7.50-7.57(1H,m), 7.63(1H,s).

MS (FAB) m/z: 655 [(M+H)⁺, Cl³⁵], 657 [(M+H)⁺, Cl³⁷].

10 [Example B-182] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[3-(thien-2-yl)propyl]piperazine
hydrochloride

In N,N-dimethylformamide (15 ml) were dissolved 1-[(5-
15 chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-[3-(thien-2-yl)propyl]piperazine (257 mg), lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate (129 mg),
1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
(131 mg) and 1-hydroxybenzotriazole hydrate (76.4 mg).

20 Under ice cooling, diisopropylethylamine (180 µl) was added
dropwise to the resulting solution, followed by stirring at
room temperature for 15.5 hours. The reaction mixture was
extracted with methylene chloride and water. The organic
layer was washed with saturated aqueous NaCl solution,
25 dried over anhydrous sodium sulfate and distilled under
reduced pressure to remove the solvent. The residue was

subjected to column chromatography (2% methanol - methylene chloride) using as a carrier silica gel. After conversion into the corresponding hydrochloride by the addition of 1N aqueous hydrochloric acid in ethanol, methylene chloride - methanol - ether was added to solidify the hydrochloride. The resulting solid was purified again by subjecting it to thin-layer chromatography (10% methanol - methylene chloride), followed by the addition of 1N aqueous hydrochloric acid in ethanol to form the corresponding hydrochloride. Methylene chloride - methanol - ether was added to solidify the hydrochloride. The resulting solid was collected by filtration, washed with ether and then dried, whereby the title compound (62.6 mg) was obtained as colorless powder.

¹H-NMR (DMSO-d₆) δ: 1.45-2.00 (4H,m), 2.30-3.80 (11H,m), 4.30-4.80 (3H,m), 5.15-5.65 (1H,m), 6.75-6.85 (1H,m), 6.85-6.95 (1H,m), 7.01 (1H,s), 7.20-7.35 (2H,m), 7.48 (1H,d,J=9.0Hz), 7.75 (1H,s), 11.42 (1H,br), 12.44 (1H,s). MS (FAB) m/z: 604 [(M+H)⁺, Cl³⁵], 606 [(M+H)⁺, Cl³⁷].

[Example B-183] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[3-(3,4-dimethoxyphenyl)propyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-182, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.40-1.90 (4H,m), 2.40-2.70 (1H,m),

2.90 (3H, s), 3.00-3.20 (2H, m), 3.30-3.80 (16H, m), 4.30-
 4.80 (3H, m), 5.20-5.60 (1H, m), 6.60-6.70 (1H, m),
 6.82 (1H, d, J=8.1 Hz), 7.01 (1H, s), 7.25-7.35 (1H, m),
 7.48 (1H, d, J=8.8 Hz), 7.70-7.80 (1H, m), 11.20-11.50 (1H, br),
 12.43 (1H, s).

MS (FAB) m/z: 658 [(M+H)⁺, Cl³⁵], 660 [(M+H)⁺, Cl³⁷].

[Example B-184] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-[(pyrrolidin-1-yl)sulfonyl]ethyl]piperazine hydrochloride

In the same manner as in Example B-182, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.80-1.90 (4H, m), 2.10-2.30 (2H, m), 2.40-3.85 (15H, m), 2.90 (3H, s), 4.30-4.90 (3H, m), 5.30-5.50 (1H, m),
 7.02 (1H, s), 7.25-7.35 (1H, m), 7.48 (1H, d, J=8.8 Hz),
 7.76 (1H, s), 11.27 (1H, br), 12.44 (1H, s).

MS (FAB) m/z: 641 [(M+H)⁺, Cl³⁵], 642 [(M+H)⁺, Cl³⁷].

[Example B-185] 1-[[6-Methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridin-2-yl]carbonyl]-4-[(1-phenylsulfonyl-5-trimethylsilylethynyl)indol-2-yl)sulfonyl]piperazine

In the same manner as in Example B-103, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 0.25-0.35 (9H, m), 2.45-2.55 (3H, m), 2.55-2.65 (2H, m), 2.65-2.75 (2H, m), 3.45-3.55 (6H, m), 3.85-3.95 (4H, m), 7.40-7.65 (6H, m), 7.70-7.75 (1H, m), 8.00-

8.05 (2H, m), 8.20-8.25 (1H, m).

MS (FAB) m/z: 665 (M+H)⁺.

[Example B-186] 1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-104, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.47 (3H, s), 2.50-2.60 (2H, m), 2.65 (2H, t, J=5.6 Hz), 3.17 (4H, t, J=5.0 Hz), 3.46 (2H, s), 3.90 (4H, br s), 6.84 (1H, s), 7.00 (1H, d, J=1.0 Hz), 7.35-7.40 (1H, m), 7.45-7.50 (1H, m), 7.87 (1H, s), 8.92 (1H, br s).

MS (FAB) m/z: 453 (M+H)⁺.

[Example B-187] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-62, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.76 (2H, br), 2.89 (3H, s), 3.05-3.10 (2H, m), 3.35-3.50 (2H, m), 3.74 (4H, br), 4.10-4.60 (2H, m), 6.97 (1H, s), 7.00-7.05 (1H, m), 7.30-7.35 (1H, m), 7.49 (1H, d, J=9.0 Hz), 7.78 (1H, d, J=2.0 Hz), 10.88 (1H, br s), 12.45 (1H, s).

MS (FAB) m/z: 463 [(M+H)⁺, Cl³⁵], 465 [(M+H)⁺, Cl³⁷].

[Example B-188] 1-[(2-tert-Butoxycarbonylisoindolin-5-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.51(9H,s), 3.13(4H,br s), 3.72(4H,br s),
4.60-4.70(4H,m), 6.96(1H,s), 7.18-7.30(3H,m), 7.31-
5 7.40(2H,m), 7.69(1H,s), 8.93(1H,s).

MS (FAB) m/z: 545 [(M+H)⁺, Cl³⁵], 547 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₂₉ClN₄O₅S·H₂O

Calculated: C, 55.46; H, 5.55; N, 9.95.

Found: C, 55.69; H, 5.35; N, 9.85.

10 [Example B-189] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-
[(isoindolin-5-yl)carbonyl]piperazine

In the same manner as in Example B-1, the title compound was obtained.

m.p. 196-199°C (dec).

15 ¹H-NMR (DMSO-d₆) δ: 3.08(4H,br s), 3.44(2H,br s),
3.69(2H,br s), 4.47(2H,s), 4.50(2H,s), 7.02(1H,s), 7.30-
7.45(4H,m), 7.51(1H,d,J=8.8Hz), 7.79(1H,d,J=2.0Hz),
9.65(2H,br s), 12.44(1H,s).

MS (FAB) m/z: 445 [(M+H)⁺, Cl³⁵], 447 [(M+H)⁺, Cl³⁷].

20 Elementary analysis for C₂₁H₂₁ClN₄O₃S

Calculated: C, 48.75; H, 5.06; Cl, 13.70; N, 10.83; S,
6.20.

Found: C, 49.06; H, 4.96; Cl, 13.61; N, 10.63; S,
6.08.

25 [Example B-190] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(2-

methylisoindolin-5-yl)carbonyl]piperazine

In the same manner as in Example B-32, the title compound was obtained.

m.p. 175-180°C (dec).

5 $^1\text{H-NMR}$ (DMSO- d_6) δ : 2.97(3H,br s), 3.09(4H,br s),
3.43(2H,br s), 3.68(2H,br s), 4.57(4H,br s), 7.02(1H,s),
7.30-7.45(4H,m), 7.51(1H,d,J=9.0Hz), 7.79(1H,s),
11.58(1H,br s), 12.46(1H,s).

MS (FAB) m/z : 459 [(M+H) $^+$, Cl 35], 461 [(M+H) $^+$, Cl 37].

10 Elementary analysis for $\text{C}_{22}\text{H}_{23}\text{ClN}_4\text{O}_3\text{S}\cdot 0.95\text{HCl}\cdot 1.6\text{H}_2\text{O}$
Calculated: C, 50.58; H, 5.24; Cl, 13.23; N, 10.72; S,
6.14.

Found: C, 50.90; H, 5.46; Cl, 13.10; N, 10.32; S,
5.97.

15 [Example B-191] 1-[(5-Chloroindol-2-yl)sulfonyl]-3-[N-(2-hydroxyethyl)carbamoylemethyl-4-(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-62, the title
20 compound was obtained.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.30-3.82(20H,m), 2.90(3H,s), 4.30-
4.50(2H,m), 4.50-4.75(1.5H,m), 5.00-5.10(0.5H,m), 5.28-
5.38(0.5H,m), 5.80-5.90(0.5H,m), 7.02(1H,s),
7.31(1H,d,J=8.8Hz), 7.48(1H,d,J=8.8Hz), 7.76(1H,s), 7.95-
25 8.05(1H,m), 11.24(0.5H,m), 11.39(0.5H,m), 12.43(1H,s).

FAB-MS m/z: 580 [(M+H)⁺-H, Cl³⁵], 582 [(M+H)⁺-H, Cl³⁷].

[Example B-192] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-(1,4-dioxo-8-azaspiro[4,5]decan-8-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.79-3.73 (22H, m), 2.89 (3H, s), 3.93 (4H, s), 4.43-4.75 (2H, m), 5.55 (1H, m), 7.01 (1H, d, J=6.1 Hz), 7.30 (1H, dd, J=1.9, 8.8 Hz), 7.49 (1H, d, J=8.8 Hz), 7.76 (1H, s), 12.45 (1H, s).

MS (FAB) m/z: 649 [(M+H)⁺, Cl³⁵], 651 [(M+H)⁺, Cl³⁷].

[Example B-193] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(1,3-dioxolan-2-yl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.77 (2H, m), 2.22 (2H, m), 2.49-3.95 (15H, m), 4.55-5.03 (3H, m), 5.66 (1H, m), 6.94 (1H, s), 7.28-7.37 (2H, m), 7.64 (1H, d, J=1.7 Hz), 9.34 (1H, s).

MS (FAB) m/z: 566 [(M+H)⁺, Cl³⁵], 568 [(M+H)⁺, Cl³⁷].

[Example B-194] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(2-1,3-dioxoisindol-2-yl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-62, the title

compound was obtained.

¹H-NMR (CDCl₃) δ: 2.42-2.45 (3H,m), 2.55-2.84 (5.5H,m), 3.31-3.57 (2H,m), 3.70-3.92 (4.5H,m), 4.42-4.51 (1H,m), 4.61 (2/3H,broad d,J=12.7Hz), 5.25 (1/3H,broad), 5.82 (1/3H,broad), 6.22 (2/3H,broad d,J=9.7Hz), 6.99 (1H,s), 7.30-7.38 (2H,m), 7.62-7.73 (5H,m), 7.79 (2/3H,m), 8.97 (1/3H,broad).

MS (FAB) m/z: 639 (M+H)⁺.

[Example B-195] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-naphthoxy)ethyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.28-2.51 (5H,m), 2.55-2.60 (2H,m), 2.78-2.87 (4H,m), 3.26-3.29 (1H,m), 3.52-3.63 (2H,m), 3.84-3.87 (2H,m), 4.06-4.19 (2H,m), 4.61 (2/3H,broad d,J=12.7Hz), 5.16 (1/3H,broad), 5.71 (1/3H,broad m), 6.22 (2/3H,broad), 6.87-6.94 (2H,m), 7.09 (1H,broad), 7.22-7.33 (3H,m), 7.39-7.43 (1H,m), 7.64-7.74 (4H,m), 9.09 (1H,broad s).

MS (FAB) m/z: 650 (M+H)⁺.

[Example B-196] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-phenoxyethyl)piperazine

In the same manner as in Example B-62, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 2.26-2.40 (2H,m), 2.47 (3H,s), 2.55-2.61 (1H,m), 2.67-2.85 (5H,m), 3.24-3.30 (1/3H,m), 3.48-3.51 (2/3H,m), 3.62-3.65 (2H,m), 3.82-4.08 (4H,m), 4.61 (2/3H,broad d,J=13.9Hz), 5.12 (1/3H,broad), 5.82 (1/3H,broad d,J=12.9Hz), 6.18 (2/3H,broad), 6.68-6.70 (1H,m), 6.87-6.92 (2H,m), 6.95 (1H,s), 7.21-7.23 (2H,m), 7.29-7.35 (2H,m), 7.65 (1H,s), 8.02 (1/3H,s), 9.03 (2/3H,broad s).

MS (FAB) m/z: 599 (M⁺, Cl³⁵), 601 (M⁺, Cl³⁷).

10 [Example B-197] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-hydroxyethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

15 ¹H-NMR (CDCl₃) δ: 1.88-1.94 (2H,m), 2.48 (3H,s), 2.41-2.62 (2H,m), 2.75-2.90 (4H,m), 3.12-3.21 (1H,m), 3.33-3.85 (6H,m), 4.66 (2/3H,broad d,J=13.7Hz), 4.88-4.90 (1/3H,m), 5.37-5.40 (2/3H,m), 6.18 (1/3H,broad d,J=13.4Hz), 6.91-6.95 (1H,m), 7.29-7.37 (2H,m), 7.65 (1H,s), 9.02 (1H,broad s).

20 MS (FAB) m/z: 524 [(M+H)⁺, Cl³⁵], 526 [(M+H)⁺, Cl³⁷].

[Example B-198] 4-(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-oxo-1,3-oxazolan-3-yl)ethyl]piperazine

25 In the same manner as in Example B-62, the title

compound was obtained.

¹H-NMR (CDCl₃) δ: 1.90 (1H, broad), 2.23-2.32 (1H, broad m),
2.48 (3H, s), 2.65 (2H, broad m), 2.80 (2H, broad s), 2.87-
2.89 (2H, broad m), 3.21-3.45 (3H, broad m), 3.56 (2H, broad m),
5 3.67 (2H, s), 3.76-4.04 (2H, broad m), 4.29-4.41 (2H, m),
4.62 (2/5H, broad d, J=10.4Hz), 4.75 (3/5H, broad),
4.62 (3/5H, broad d, J=14.6Hz), 5.90 (2/5H, broad), 6.97 (1H, s),
7.29 (1H, dd, J=1.9, 8.7Hz), 7.41 (1H, broad m), 7.63 (1H, s).

MS (FAB) m/z: 593 (M+H)⁺.

10 [Example B-199] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(5,6-
dimethyl-4,5,6,7-tetrahydrothiazolo[4,5-d]pyridazin-2-
yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-82, the title
compound was obtained.

15 ¹H-NMR (DMSO-d₆) δ: 2.65 (3H, br s), 2.76 (3H, br s),
3.13 (4H, br s), 3.74 (2H, br s), 4.10-4.50 (6H, br),
7.03 (1H, d, J=1.5Hz), 7.31 (1H, dd, J=8.8, 2.0Hz),
7.48 (1H, d, J=8.8Hz), 7.76 (1H, d, J=2.0Hz), 12.42 (1H, br s).
MS (FAB) m/z: 495 [(M+H)⁺, Cl³⁵], 497 [(M+H)⁺, Cl³⁷].

20 [Example B-200] 2-[[[4-tert-Butoxycarbonylpiperazin-1-
yl)carbonyl]methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-
methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazine

In the same manner as in Example B-79, the title
25 compound was obtained.

¹H-NMR (CDCl₃) δ: 1.49 (9H, s), 2.49 (3H, s), 2.55-3.20 (8H, m),
 3.30-3.85 (12H, m), 3.95-4.04 (0.5H, m), 4.10-4.18 (0.5H, m),
 4.55-4.67 (0.5H, m), 4.95-5.07 (0.5H, m), 5.55-5.65 (0.5H, m),
 6.00-6.10 (0.5H, m), 7.00 (1H, s), 7.25-7.31 (1H, m),
 5 7.37 (1H, d, J=8.8Hz), 7.65 (1H, s).

MS (FAB) m/z: 706 [(M+H)⁺, Cl³⁵], 708 [(M+H)⁺, Cl³⁷].

[Example B-201] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(piperazin-1-yl)carbonyl]methyl]piperazine
 10 hydrochloride

In the same manner as in Example B-1, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.50-3.85 (23H, m), 4.30-4.45 (1H, m),
 4.60-4.75 (0.5H, m), 5.00-5.10 (0.5H, m), 5.30-5.40 (0.5H, m),
 15 5.80-5.95 (0.5H, m), 7.03 (1H, s), 7.32 (1H, d, J=8.8Hz),
 7.50 (1H, d, J=8.8Hz), 7.78 (1H, s), 9.20-9.45 (1H, br),
 12.46 (1H, br s).

MS (FAB) m/z: 606 [(M+H)⁺, Cl³⁵], 608 [(M+H)⁺, Cl³⁷].

[Example B-202] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N-furfurylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
 20 hydrochloride

In the same manner as in Example B-79, the title compound was obtained.

25 ¹H-NMR (DMSO-d₆) δ: 2.50-3.50 (13H, m), 3.60-3.85 (2H, m),

4.12-4.50 (3H,m), 4.60-4.75 (0.5H,m), 5.05-5.10 (0.5H,m),
 5.30-5.40 (0.5H,m), 5.78-5.90 (0.5H,m), 6.17-6.25 (1H,br),
 6.35-6.42 (1H,m), 7.03 (1H,s), 7.31 (1H,d,J=8.8Hz),
 7.48 (1H,d,J=8.8Hz), 7.51-7.58 (1H,m), 7.77 (1H,s), 8.41-
 5 8.55 (1H,br), 12.44 (1H,br s).

MS (FAB) m/z: 617 [(M+H)⁺, Cl³⁵], 619 [(M+H)⁺, Cl³⁷].

HRMS (FAB) m/z: 617.1418 (M+H)⁺ (calcd for C₂₇H₂₉ClN₆O₅S₂,
 617.1408).

[Example B-203] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N-
 10 methoxy-N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
 hydrochloride

In the same manner as in Example B-79, the title
 compound was obtained.

15 ¹H-NMR (DMSO-d₆) δ: 2.50-3.83 (20H,m), 4.30-4.80 (2.5H,br),
 5.07 (0.5H,br s), 5.31-5.36 (0.5H,br), 5.78 (0.5H,br s),
 7.03 (1H,s), 7.31 (1H,d,J=9.2Hz), 7.48 (1H,d,J=9.2Hz),
 7.77 (1H,s), 11.04 (1H,br s), 12.45 (1H,br s).

MS (FAB) m/z: 581 [(M+H)⁺, Cl³⁵], 583 [(M+H)⁺, Cl³⁷].

20 [Example B-204] 1-[(6-(tert-Butoxycarbonyl)-4,5,6,7-
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-
 chloroindol-2-yl)sulfonyl]piperazine

In the same manner as in Example B-62, the title
 compound was obtained.

25 ¹H-NMR (CDCl₃) δ: 1.48 (9H,s), 2.85 (2H,br s), 3.22 (4H,br s),

3.73(2H,br s), 3.89(2H,br s), 4.58(2H,br s), 4.65(2H,br s),
6.97(1H,s), 7.32(1H,dd,J=8.8,2.0Hz), 7.37(1H,d,J=8.8Hz),
7.66(1H,d,J=2.0Hz), 8.72(1H,s).

MS (FAB) m/z: 566 [(M+H)⁺, Cl³⁵], 568 [(M+H)⁺, Cl³⁷].

5 [Example B-205] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-
[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-1, the title
compound was obtained.

10 ¹H-NMR (DMSO-d₆) δ: 3.01(2H,t,J=6.1Hz), 3.13(4H,br s),
3.44(2H,t,J=6.1Hz), 3.75(2H,br s), 4.36(2H,br s),
4.42(2H,s), 7.04(1H,s), 7.31(1H,dd,J=8.8,2.0Hz),
7.49(1H,d,J=8.8Hz), 7.77(1H,d,J=2.0Hz), 9.46(2H,br s),
12.43(1H,s).

15 MS (FAB) m/z: 466 [(M+H)⁺, Cl³⁵], 468 [(M+H)⁺, Cl³⁷].

[Example B-206] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-
hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazine

20 In the same manner as in Example B-144, the title
compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.70-3.05(2H,br), 3.05-3.25(6H,br),
3.65-4.50(6H,br), 7.03(1H,s), 7.30(1H,dd,J=8.8,2.0Hz),
7.47(1H,d,J=8.8Hz), 7.76(1H,d,J=2.0Hz), 8.35(1H,s),
12.40(1H,s).

25 MS (FAB) m/z: 482 [(M+H)⁺, Cl³⁵], 484 [(M+H)⁺, Cl³⁷].

[Example B-207] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(ethoxycarbonyl)methyl]-1-[(6-methylsulfonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In a saturated solution of hydrochloride in ethanol
5 was dissolved 1-(tert-butoxycarbonyl)-4-[(5-chloroindol-2-yl)sulfonyl]-2-[(methoxycarbonyl)methyl]piperazine (1.15 g), followed by stirring at room temperature for 1 hour. The solvent was distilled off under reduced pressure. Methylene chloride and a saturated aqueous solution of
10 sodium bicarbonate were added to the residue to separate into layers. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. A portion (519 mg) of the residue (0.97 g) was dissolved in N,N-dimethylformamide (2 ml),
15 followed by the addition of lithium (6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carboxylate (328 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (288 mg) and 1-hydroxybenzotriazole (363 mg). The resulting mixture was stirred at room temperature for 3
20 days. Methylene chloride and water were added and the organic layer was collected. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by flash column chromatography (hexane : ethyl acetate =
25 1:1) using as a carrier silica gel.

The resulting purified product was dissolved in a

saturated solution (5 ml) of hydrochloride in ethanol, followed by stirring at room temperature for 1 hour. After the addition of methylene chloride, the resulting mixture was washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in methylene chloride (5 ml), followed by the addition of methanesulfonyl chloride (105 μ l) and triethylamine (0.5 ml). The resulting mixture was stirred at room temperature for 15 minutes and washed with water. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by flash column chromatography (methylene chloride : methanol = 49:1) using as a carrier silica gel, whereby the title compound (207 mg) was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.07-1.16(3H,m), 2.67-2.90(5H,m), 2.96(3H,s), 3.20-3.24(2H,m), 3.53-3.78(4H,m), 3.95-4.04(2H,m), 4.39, 5.04(1H,each d,J=14.4,14.9Hz), 4.55(2H,s), 5.03, 5.95(1H,each br s), 7.03(1H,s), 7.31(1H,dd,J=8.8,1.7Hz), 7.47(1H,d,J=8.8Hz), 7.76(1H,d,J=1.7Hz), 12.41(1H,s).

MS (FAB) m/z : 630 ($\text{M}+\text{H}$) $^+$.

[Example B-208] 2-[Carboxymethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methylsulfonyl-4,5,6,7-

tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-77, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.32-3.74 (14H, m), 4.38, 5.37 (1H, each
 5 d, J=12.2, 12.4 Hz), 4.54 (2H, s), 5.00, 5.83 (1H, each br s),
 7.02 (1H, s), 7.30 (1H, d, J=8.8 Hz), 7.47 (1H, d, J=8.8 Hz),
 7.75 (1H, s), 12.51 (1H, s).

HRMS (FAB) m/z: 602.0612 (M+H)⁺ (calcd for C₂₂H₂₅N₅O₇ClS₃,
 602.0605).

10 [Example B-209] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[N-methylsulfonyl]carbamoyl]methyl]-1-[(6-methylsulfonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine

In tetrahydrofuran (5 ml) was dissolved 2-
 15 [carboxymethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methylsulfonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine (115 mg), followed by the addition of carbonyldiimidazole (58 mg). The resulting mixture was heated under reflux for 2 hours. After cooling to room
 20 temperature, methanesulfonamide (34 mg) and 1,8-diazabicyclo[5.4.0]-7-undecene (55 mg) were added, followed by stirring for 1.5 hours. The solvent was distilled off under reduced pressure. The residue was dissolved in methylene chloride and the solution was washed with water,
 25 0.2N hydrochloric acid and saturated aqueous NaCl solution. The organic layer was dried over anhydrous sodium sulfate

and distilled under reduced pressure to remove the solvent. The residue was purified by preparative TLC (methylene chloride : methanol = 9:1). The solvent was distilled off under reduced pressure. The solid thus obtained was washed with ether, whereby the title compound (62 mg) was obtained as a colorless solid.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.50-3.56 (15H,m), 3.65-3.77 (2H,m), 4.40, 5.40 (1H, each d, $J=15.4, 11.8\text{Hz}$), 4.55 (2H,s), 5.10, 5.98 (1H, each br s), 7.04 (1H,s), 7.31 (1H,d, $J=8.8, 2.0\text{Hz}$), 7.47 (1H,d, $J=8.8\text{Hz}$), 7.76 (1H,d, $J=2.0\text{Hz}$), 11.88 (1H,s), 12.44 (1H,s).

MS (FAB) m/z : 602 ($\text{M}+\text{H}$) $^+$.

[Example B-210] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

To a solution of lithium 6-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate (1.89 g) in N,N -dimethylformamide (40 ml) were added 1-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazine (2.50 g), 1-hydroxybenzotriazole monohydrate (1.20 g) and 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.70 g) at room temperature. After stirring for 2 days, ethyl acetate (200 ml) and water (1.0 l) were added to the reaction mixture to separate it into layers. The water layer was extracted with ethyl acetate (2 x 150 ml). The organic layers were combined, washed with water (1.0 l) and

a saturated aqueous solution (200 ml) of sodium bicarbonate, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 200 g, methylene chloride : ethyl acetate = 7:1 → 1:1), whereby 1-[[6-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazine was obtained as pale yellow foam. A solution of the boc form in methylene chloride (15 ml) was added trifluoroacetic acid (15 ml) at room temperature. After stirring for 10 minutes, the solvent was distilled off under reduced pressure. Methylene chloride (50 ml) and a saturated aqueous solution (150 ml) of sodium bicarbonate were added to the residue to separate it into layers. The water layer was extracted with methylene chloride (6 x 25 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 100 g, methylene chloride : methanol = 25:1 → 10:1), whereby the title compound (754 mg) was obtained as a pale brown solid.

¹H-NMR (DMSO-d₆) δ: 2.67(2H,t,J=5.7Hz), 2.96(2H,t,J=5.7Hz), 3.18(4H,t,J=4.9Hz), 3.31(1H,s), 3.77(2H,br s), 3.90(2H,s), 4.44(2H,br s), 7.57(1H,dd,J=8.8,2.0Hz), 8.05(1H,d,J=8.8Hz),

8.09 (1H, s), 8.31 (1H, d, J=2.0 Hz).

MS (FAB) m/z: 483 (M+H)⁺.

[Example B-211] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-
4-[[6-(pyridin-4-yl)-4,5,6,7-tetrahydrothiazolo[5,4-
5 c]pyridin-2-yl]carbonyl]piperazine hydrochloride

To a solution of 1-[(6-chlorobenzo[b]thien-2-
yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-
2-yl]carbonyl]piperazine (200 mg) in N,N-dimethylformamide
(2.0 ml) were added 4-bromopyridine (87.0 mg) and

10 triethylamine (150 μ l) at room temperature. The resulting
mixture was stirred under heat at 120°C for 12 hours.

After concentration of the reaction mixture, methylene
chloride (20 ml), a saturated aqueous solution (50 ml) of
sodium bicarbonate and water (50 ml) were added to the
15 concentrate to separate it into layers. The water layer
thus obtained was extracted with methylene chloride (4 x 20
ml). The organic layers were combined, dried over
anhydrous sodium sulfate and distilled under reduced
pressure to remove the solvent. The residue was purified

20 by preparative thin-layer chromatography (methylene
chloride : methanol = 20:1) using silica gel, followed by
purification by preparative thin-layer chromatography
(methylene chloride : acetone : methanol = 15:5:1) using
silica gel. The purified product was dissolved in

25 methylene chloride, methanol and 1N hydrochloric acid. The
resulting solution was concentrated under reduced pressure

and dried, whereby the title compound (56.5 mg) was obtained as a pale yellow solid.

¹H-NMR (DMSO-d₆) δ: 2.97(2H,t,J=5.6Hz), 3.17(4H,br s),
3.77(2H,br s), 4.05(2H,t,J=5.6Hz), 4.41(2H,br s),
5.01(2H,s), 7.31(2H,br s), 7.56(1H,d,J=8.4Hz),
8.05(1H,d,J=8.4Hz), 8.08(1H,s), 8.30(2H,s), 8.32(1H,s),
13.70(1H,br s).

MS (FAB) m/z: 560 (M+H)⁺.

[Example B-212] 2-(Methoxycarbonylmethyl)-1-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-
[[5-(trimethylsilyl)ethynyl]indol-2-yl]sulfonyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 0.26(9H,s), 2.49(3H,s), 2.53-2.68(1H,m),
2.74(1H,dd,J=12.0,2.7Hz), 2.77-2.83(3H,m), 2.87(2H,br s),
3.00(1H,dd,J=15.8,8.7Hz), 3.11-3.26(1/2H,br), 3.39-
3.54(1/2H,br), 3.59-3.67(5H,m), 3.72-3.96(2H,m),
4.61(1/2H,br d,J=13.2Hz), 5.22(1/2H,br s), 5.71(1/2H,br
d,J=13.2Hz), 6.16(1/2H,br s), 6.97(1H,s),
7.34(1H,d,J=8.6Hz), 7.43(1H,dd,J=8.6,1.5Hz), 7.81(1H,s),
9.35(1H,br d,J=11.0Hz).

MS (FAB) m/z: 614 (M+H)⁺.

[Example B-213] 4-[(5-Ethynylindol-2-yl)sulfonyl]-2-
(methoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-104, the title compound was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.49(3H,s), 2.53-2.95(7H,m), 2.95-3.05(1H,m), 3.04(1H,s), 3.20(1/2H,br t, J =11.6Hz),
 5 3.46(1/2H,br t, J =11.6Hz), 3.59-3.75(5H,m), 3.75-3.97(2H,m),
 4.62(1/2H,br d, J =12.8Hz), 5.22(1/2H,br s), 5.73(1/2H,br d, J =13.6Hz), 6.18(1/2H,br s), 7.00(1H,s),
 7.37(1H,d, J =8.6Hz), 7.45(1H,dd, J =8.6,1.2Hz), 7.85(1H,s),
 9.28(1H,br d, J =13.2Hz).

10 MS (FAB) m/z : 542 ($\text{M}+\text{H}$) $^+$.

[Example B-214] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(morpholin-4-yl)sulfonyl]ethyl]piperazine hydrochloride

15 In the same manner as in Example B-182, the title compound was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.10-2.40(2H,m), 2.50-2.80(2H,m),
 2.90(3H,s), 3.00-3.30(8H,m), 3.30-3.90(9H,s), 4.30-4.90(3H,m), 5.30-5.50(1H,m), 7.03(1H,s),
 20 7.31(1H,dd, J =8.8,1.5Hz), 7.48(1H,d, J =8.8Hz),
 7.76(1H,d, J =1.5Hz), 11.42(1H,br), 12.45(1H,s).

MS (FAB) m/z : 657 [$(\text{M}+\text{H})^+$, Cl^{35}], 659 [$(\text{M}+\text{H})^+$, Cl^{37}].

[Example B-215] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-ethoxycarbonyl)ethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

25

In the same manner as in Example B-62, the title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.15-1.25(3H,m), 1.40-1.80(1H,m), 2.05-2.15(1H,m), 2.25-2.45(3H,m), 2.49(3H,s), 2.50-3.55(6H,m),
 3.67(2H,s), 3.70-3.90(2H,m), 4.00-4.20(2H,m), 4.55-6.10(2H,m), 6.95(1H,s), 7.30-7.40(2H,m),
 7.65(1H,d,J=1.6Hz), 9.03(1H,br).

MS (FAB) m/z: 580 [(M+H)⁺, Cl³⁵], 582 [(M+H)⁺, Cl³⁷].

[Example B-216] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[2-(morpholin-4-yl)carbonyl]ethyl]piperazine

In the same manner as in Referential Example 319, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.85-2.00(1H,m), 2.05-2.20(1H,m), 2.20-2.35(2H,m), 2.55-2.70(1H,m), 3.80-2.95(4H,m), 3.00-3.80(14H,m), 4.25-5.55(5H,m), 7.02(1H,s),
 7.30(1H,dd,J=8.8,2.0Hz), 7.48(1H,d,J=8.8Hz),
 7.75(1H,d,J=2.0Hz), 11.45(1H,br s), 12.43(1H,s).

MS (FAB) m/z: 621 [(M+H)⁺, Cl³⁵], 623 [(M+H)⁺, Cl³⁷].

[Example B-217] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[2-(N,N-dimethylaminocarbonyl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Referential Example 319, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.85-2.00 (1H,m), 2.05-2.20 (1H,m), 2.20-2.35 (2H,m), 2.50-2.65 (1H,m), 2.70-3.80 (17H,m), 4.30-5.55 (4H,m), 7.02 (1H,s), 7.29 (1H,dd,J=8.8,2.0Hz), 7.48 (1H,d,J=8.8Hz), 7.75 (1H,d,J=2.0Hz), 11.49 (1H,br s),
 5 12.44 (1H,s).

MS (FAB) m/z: 579 [(M+H)⁺, Cl³⁵], 581 [(M+H)⁺, Cl³⁷].

[Example B-218] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

10 In the same manner as in Example B-182, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.90-2.18 (2H,m), 2.20-2.90 (4H,m), 2.90 (3H,s), 3.12 (2H,br s), 3.21-3.82 (6H,m), 4.30-4.85 (2H,m), 5.31-5.43 (0.5H,m), 5.55-5.70 (0.5H,m),
 15 7.02 (1H,d,J=2.0Hz), 7.31 (1H,dd,J=8.9,2.1Hz), 7.48 (1H,d,J=8.8Hz), 7.76 (1H,d,J=1.7Hz), 11.18 (1H,br s), 12.44 (1H,br s).

MS (FAB) m/z: 533 [(M+H)⁺, Cl³⁵], 535 [(M+H)⁺, Cl³⁷].

[Example B-219] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6,6-ethylenedioxy-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)carbonyl]piperazine
 20

In the same manner as in Example B-62, the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 1.93 (2H,t,J=6.6Hz), 2.73-3.32 (10H,m),
 25 3.73 (1H,br s), 3.93 (4H,s), 3.95 (1H,br s), 6.97, 7.03 (1H,s),

7.30 (1H, dd, J=8.8, 2.2 Hz), 7.45-7.47 (1H, m), 7.76 (1H, s).

MS (FAB) m/z: 523 [(M+H)⁺, Cl³⁵], 525 [(M+H)⁺, Cl³⁷].

[Example B-220] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)carbonyl]piperazine

In a 300-mL egg-plant type flask was charged 1-[(5-chloroindol-2-yl)sulfonyl]-4-[(6,6-ethylenedioxy-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)carbonyl]piperazine (740 mg), followed by dissolution in methanol (150 mL). To the resulting solution was added p-toluenesulfonic monohydrate (100 mg), followed by heating under reflux. After 16 hours, the reaction was terminated and the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (silica gel: 75 g, ethyl acetate : hexane = 1:1), whereby the title compound (110 mg) was obtained as a pale yellow amorphous solid.

¹H-NMR (CDCl₃) δ: 2.76 (2H, t, J=6.8 Hz), 3.18 (2H, t, J=6.8 Hz), 3.19-3.22 (6H, m), 3.65 (2H, s), 3.89 (1H, br s), 4.59 (1H, br s), 6.97 (1H, s), 7.31-7.39 (2H, m), 7.66 (1H, d, J=2.0 Hz).

MS (FAB) m/z: 479 [(M+H)⁺, Cl³⁵], 481 [(M+H)⁺, Cl³⁷].

[Example B-221] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(4,5-dihydro-7H-pyrano[4,3-d]thiazol-2-yl)carbonyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

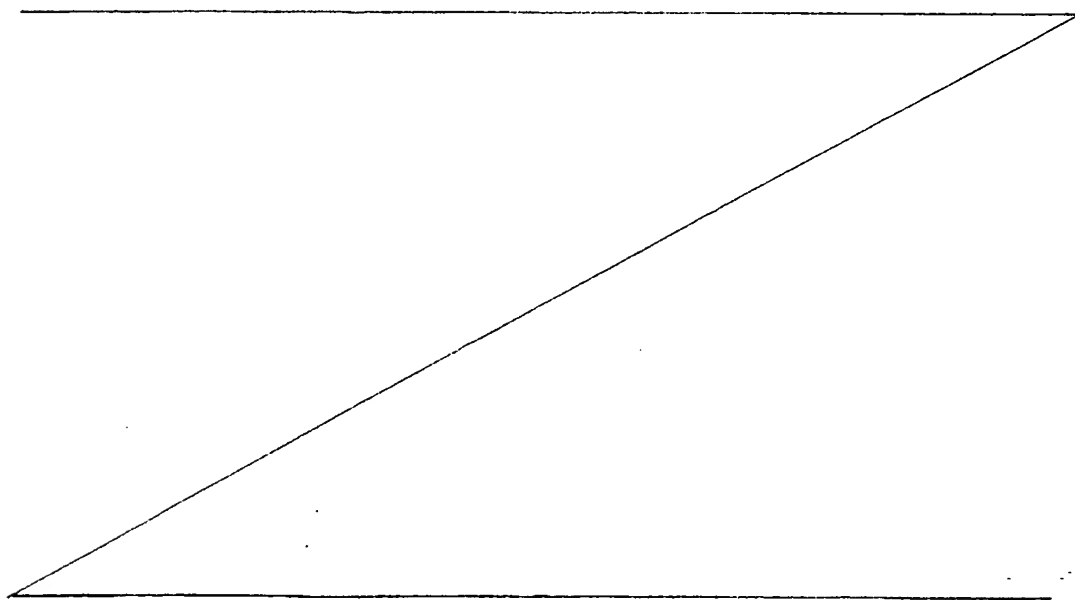
¹H-NMR (DMSO-d₆) δ: 2.82 (2H, t, J=5.6 Hz), 3.12 (4H, t, J=4.9 Hz),

3.28-3.35 (2H, m), 3.73 (1H, br s), 3.93 (2H, t, $J=5.6\text{Hz}$),
4.39 (1H, br s), 4.79 (2H, s), 7.03 (1H, s),
7.30 (1H, dd, $J=8.8, 2.2\text{Hz}$), 7.47 (1H, d, $J=8.8\text{Hz}$), 7.76 (1H, s).
MS (FAB) m/z : 467 $[(M+H)^+, Cl^{35}]$, 469 $[(M+H)^+, Cl^{37}]$.

- 5 [Example B-222] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[N-(phenylsulfonyl)carbamoyl]methyl]piperazine hydrochloride

10 In the same manner as in Example B-62, the title compound was obtained.

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 2.52-3.77 (12H, m), 3.88-4.20 (2H, m),
4.24-4.48 (1.5H, m), 4.52-4.75 (1H, m), 5.00 (0.5H, m), 5.23-
5.32 (0.5H, m), 5.57 (0.25H, br s), 5.79 (0.25H, br s),
6.97 (1H, s), 7.28 (1H, d, $J=8.8\text{Hz}$), 7.45 (1H, d, $J=8.8\text{Hz}$), 7.49-



7.53(1H,m), 7.61(2H,br s), 7.72(1H,s), 7.85(2H,br s),
11.54-11.98(1H,m), 12.20-12.50(2H,m).

MS (FAB) m/z: 677 [(M+H)⁺, Cl³⁵], 679 [(M+H)⁺, Cl³⁷].

[Example B-223] 1-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N-
5 methyl-N-methylsulfonylcarbamoyl)methyl]-4-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-62, the title
compound was obtained.

10 ¹H-NMR (DMSO-d₆) δ: 3.12-4.53(21H,m), 3.75-3.82(0.5H,m),
4.35-4.45(1H,m), 5.09(0.5H,br s), 5.32-5.49(0.5H,m),
5.85(0.5H,br s), 7.02(1H,s), 7.30(1H,dd,J=8.8,2.0Hz),
7.47(1H,dd,J=8.8,2.0Hz), 7.75(1H,s), 12.44(1H,br s).

MS (FAB) m/z: 629 [(M+H)⁺, Cl³⁵], 631 [(M+H)⁺, Cl³⁷].

15 [Example B-224] 4-(5-Chloroindol-2-yl)sulfonyl]-2-[(2-
methylsulfonylhydrazino)carbonylmethyl]-1-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazine hydrochloride

20 In the same manner as in Example B-62, the title
compound was obtained.

¹H-NMR (DMSO-d₆) δ: 3.10-4.60(17H,m), 5.10-5.25(1.5H,m),
5.40-5.55(1H,m), 5.90(0.5H,br s), 6.11-6.20(0.5H,m),
6.74(0.5H,br s), 7.81(1H,s), 8.10(1H,d,J=8.6Hz),
8.27(1H,d,J=8.6Hz), 8.56(1H,s), 10.15-10.25(1H,m),
25 11.08(1H,s), 11.99(1H,s), 13.22(1H,s).

MS (FAB) m/z: 630 [(M+H)⁺, Cl³⁵], 632 [(M+H)⁺, Cl³⁷].

[Example B-225] 1-[[5(6)-chlorobenzimidazol-2-yl-
]sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-
c]pyridin-2-yl)carbonyl]piperazine

5 1-[[5(6)-chlorobenzimidazol-2-yl-]sulfonyl]pyperazine
(225 mg), 1-hydroxybenztriazole (11 mg) and 1-ethyl-3-(3-
dimethylaminopropyl)-carbodiimide (148 mg) were
successively added to a N,N-dimethylformamide solution
(3.0 ml) containing lithium 6-methyl-4,5,6,7-
10 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carboxylate (153 mg),
and stirred at room temperature for 28 hours. After
concentration under reduced pressure, the reaction solution
was divided into two layers by adding a dichloromethane and
saturated sodium chloride solution. The organic layer was
15 washed with a saturated sodium chloride solution, dried
over sodium sulfate, and concentrated under reduced
pressure. The obtained product was purified by
chromatography on a silica gel column
(dichloromethane:methanol = 20:1), concentrated by adding
20 ethanol (2 ml) and a 1N aqueous hydrochloride in ethanol
(1.5 ml), and dried. Thus, the title compound (168 mg) was
obtained as colorless amorphous.

IR (KBr) cm⁻¹ 1622, 1429, 1365, 1279, 1157, 1055, 1005, 970,
939, 922.

25 ¹H-NMR (DMSO-d₆) δ, 2.90 (3H, s), 3.03-4.00 (10H, br), 4.40
(3H, br s), 4.63-4.77 (1H, m), 7.40 (1H, dd, J = 8.8, 2.0

Hz), 7.72 (1H, d, J = 8.8 Hz), 7.78 (1H, s), 11.48-11.65 (1H, br s).

MS (FAB) m/z 481 [(M + H)⁺, Cl³⁵], 483 [(M + H)⁺, Cl³⁷].

[Test 1] Measurement of FXa inhibitory action (IC₅₀)

5 In a 96-well microtiter plate, 10 µl of a sample solution, 40 µl of a 100 mM tris · 200mM sodium chloride · 0.2% BSA (pH: 7.4) buffer and 10 µl of 0.05 U/ml human FXa ("Cosmobio-ERL HFXa-1011", dissolved in and diluted with a measuring buffer) were poured in portions, followed by the
10 addition of 40 ml of 750 µM S2222 (product of Chromogenix). An increase (mOD/min) in the absorbance at 405 nm was measured at room temperature. From the below-described equation, an inhibitory ratio % of each sample was determined. On a logarithmic probability paper, the final
15 concentration of the sample and inhibitory ratio % were plotted along the abscissa and the ordinate, respectively, whereby a 50% inhibitory concentration (IC₅₀) was determined.

 Inhibitory ratio (%) = (1 - OD of sample ÷ OD of
20 control) x 100
 (Results)

 The compound of the formula (I) having, in the structure thereof, an unsubstituted pyridylphenyl group as the group Q¹-Q²- and a 7-chloronaphthyl, 5-
25 chlorobenzofuranyl, 6-chlorobenzofuranyl, 5-chlorobenzothienyl or 5-chloro-1-methylindole group as the

group Q^A is found to have FXa activity 50% inhibitory concentration (IC₅₀) of 100 nM or greater (refer to Table 1).

Table 1

Sample compound	Concentration (nM) of the sample at which 50% of Fxa activity is inhibited
Compound of Example A-1	123
Compound of Example A-17	180
Compound of Example A-83	2800
Compound of Example A-85	1000
Compound of Example A-86	>10000
Compound of Example A-91	7000
Compound of Example A-96	450
Compound of Example A-106	420

5

The compound similar to the compound of Example A-1 except for having a substituted pyridylphenyl group, pyridylpyrimidinyl group, pyridylpyrazyl group or pyridylpyridyl group instead of the pyridylphenyl group is found to have FXa inhibitory action improved by several times as much as that of the compound of Example A-1 (refer to Table 2).

10

Table 2

Sample compound	Concentration (nM) of the sample at which 50% of Fxa activity is inhibited
Compound of Example A-152	38
Compound of Example A-155	28
Compound of Example A-123	23
Compound of Example A-137	60
Compound of Example A-4	54

The compound similar to that of Example A-1 except for having, as the group Q^A, a 6-chlorobenzothienyl group, 5-ethynylindolyl group or 5-chloroindolyl group instead of chloronaphthyl group is found to be particularly excellent in FXa inhibitory action (refer to Table 3).

Table 3

Sample compound	Concentration (nM) of the sample at which 50% of Fxa activity is inhibited
Compound of Example A-90	16
Compound of Example A-101	9.5
Compound of Example A-103	27
Compound of Example A-181	15
Compound of Example A-97	82
Compound of Example A-98	125

The compound having, as the group Q¹-Q²-, a

pyridylphenyl group is found to show a drastic improvement in the FXa inhibitory action when the nitrogen atom on the pyridine ring has been converted into N-oxide and the group Q^A represents a 6-chlorobenzothienyl group, 5-ethynylyndolyl group or 5-chloroindolyl group (refer to Table 4).

Table 4

Sample compound	Concentration (nM) of the sample at which 50% of Fxa activity is inhibited
Compound of Example A-107	4.7
Compound of Example A-117	10.5
Compound of Example A-109	6.9
Compound of Example A-116	8.6
Compound of Example A-181	2.9
Compound of Example A-120	14

The compound having, as the group Q^1-Q^2 -, a heteroaryl group such as pyridylpyrimidinyl, pyridylpyrazinyl or pyridylthiazolyl group and, as the group Q^A , a 6-chlorobenzothienyl, 6-ethynylbenzothienyl, 5-chloroindolyl or 5-ethynylyndolyl group is found to be improved in FXa inhibitory action (refer to Table 5).

Table 5

Sample compound	Concentration (nM) of the sample at which 50% of Fxa activity is inhibited
Compound of Example A-132	5.6
Compound of Example A-133	10
Compound of Example A-105	2.4
Compound of Example A-134	4.6
Compound of Example A-138	5
Compound of Example A-140	6.8
Compound of Example A-131	19
Compound of Example A-135	14
Compound of Example A-183	4.7
Compound of Example A-185	6.3
Compound of Example A-186	1.9
Compound of Example A-229	1.6
Compound of Example A-231	2.3
Compound of Example A-239	3.5
Compound of Example A-216	15
Compound of Example A-296	1.3

The compound having one or two substituents introduced in the group Q³ is found to exhibit strong FXa inhibitory activity (refer to Table 6).

Table 6

Sample compound	Concentration (nM) of the sample at which 50% of Fxa activity is inhibited
Compound of Example A-130	3.6
Compound of Example A-173	10
Compound of Example A-105	20
Compound of Example A-224	7.6
Compound of Example A-259	3.5
Compound of Example A-277	2.7
Compound of Example A-279	10
Compound of Example A-293	1.9
Compound of Example A-298	0.7

Compounds of Examples B-32, B-54, B-61, B-63 and B-99 exhibited FXa 50% inhibitory concentrations of 20 nM, 5.0 nM, 30 nM, 12.5 nM and 1.7nM, respectively.

[Test 2] Measurement of thrombin inhibitory action (IC₅₀)

In a 96-well microtiter plate, 10 μ l of a sample solution, 40 μ l of a 100 mM tris · 200mM sodium chloride · 0.2% BSA (pH: 7.4) buffer and 10 μ l of 4 U/ml human thrombin (Sigma Chemical, dissolved in and diluted with a measuring buffer) were poured in portions, followed by the addition of 40 μ l of 500 μ M S2266 (product of Chromogenix). An increase (mOD/min) in the absorbance at 405 nm was measured at room temperature. From the below-described equation, an inhibitory ratio % of each sample was

determined. On a logarithmic probability paper, the final concentration of the sample and inhibitory ratio % were plotted along the abscissa and the ordinate, respectively, whereby a 50% inhibitory concentration (IC₅₀) was found.

5 Inhibitory ratio (%) = (1 - OD of sample ÷ OD of control) x 100

 The compound having, in the structure thereof, a heteroaryl group such as pyridylpyrimidinyl or pyridylpyrazinyl, a 6-chlorobenzothienyl group, a 6-ethynylbenzothienyl, a 5-ethynylindolyl group or a 5-chloroindolyl group; or the compound having, in the structure thereof, a 6-chlorobenzothienyl, 6-ethynylbenzothienyl, 5-ethynylindolyl or 5-chloroindolyl group, in addition to a heteroaryl group such as pyridylpyrimidinyl or pyridylpyrazinyl is found to exhibit markedly low thrombin-activity inhibitory action compared with excellent FXa inhibitory action (refer to Tables 7 and 8).

10

15

Table 7

Sample compound	Concentration (nM) of the sample at which 50% of thrombin activity is inhibited
Compound of Example A-117	4100
Compound of Example A-137	4100
Compound of Example A-123	16000
Compound of Example A-109	1550
Compound of Example A-132	> 100000
Compound of Example A-133	7700
Compound of Example A-216	>50000

Table 8

Sample compound	Concentration (nM) of the sample at which 50% of thrombin action is inhibited
Compound of Example A-105	19000
Compound of Example A-134	10200
Compound of Example A-138	5900
Compound of Example A-140	1370
Compound of Example A-103	2220

5 The compound of Example B-54 exhibited a thrombin 50% inhibitory concentration of 1.05 μ M.

[Test 3] Measurement of coagulation extending action
(measurement of prothrombin time)

10 Plasma (20 μ l) and 20 μ l of a sample solution were mixed. To the resulting mixture, 40 ml of cynplastin

(product of Organon Teknika) was added and the coagulation time was measured. The concentration of the sample (CT2) at which the coagulation time of the plasma was increased twice was found and it was designated as an index of anticoagulant action.

The compound of Example 33 showed CT2 of 0.35 μ M.

[Test 4] Test of oral administration

1) Method

A sample was dissolved or suspended in a 0.5% (w/v) methyl cellulose solution and the resulting solution or suspension was orally administered (10 ml/kg) to a 8 to 11 week-old rat (Wistar male rat (Nippon SLC Co., Ltd.)) which had been fasted overnight. After administration of the sample, the blood to which 1/10 part by weight of 3.13% (w/v) sodium citrate had been added was collected from the cervical vein under anesthesia with halothane. The rat was awakened except during the blood collection. Feeding was re-started 6 hours after the blood collection. From each blood sample, the plasma was separated by centrifugal separation and anti-FXa activity in the blood and prothrombin time extending action were measured.

2) Measuring method

2-1) Measurement of anti-FXa activity in the plasma

In a 96-well plate, 5 μ l of the plasma was poured in portions, followed by the addition of 55 μ l of a 8:1:2 mixture of 100 mM tris · 200 mM sodium chloride · 0.2% BSA

(pH 7.4) buffer, water and 0.1 U/ml human Factor Xa solution (dissolved in and diluted with a measuring buffer) and 40 μ l of 750 μ M S-2222. After stirring for 10 seconds in a plate mixer, an increase (mOD/min) of the absorbance at 405 nm was measured at room temperature. The inhibitory ratio was calculated as follows:

An inhibitory ratio (%) = $(1 - \text{OD of sample} \div \text{OD of control on average relative to blood-collecting time of sample}) \times 100$

2-2) Measurement of coagulation extending action in oral administration (measurement of prothrombin time)

To 20 μ l of the plasma, 40 μ l of cynplastin (Organon Teknika/USA) was added and the coagulation time was measured. The ratio of the prothrombin time after the administration of the sample relative to the prothrombin time before the administration of the sample was designated as an index of the coagulation extending action.

3) Results

The compound of Example A-60 showed an anti-FXa activity of 70% in the plasma one hour after the oral administration of 30 mg/kg of the sample. It extended the prothrombin time by 1.18 times.

The compound of Example B-36 showed an anti-FXa activity of 68% in the plasma one hour after the oral administration of 30 mg/kg of the sample. It extended the thrombin time.

[Test 5] Testing method of anti-thrombus effects in a tissue thromboplastin-derived rat DIC model

A rat was anesthetized with halothane. After the collection of the blood (for measurement of the number of platelets, anti-FXa activity and TAT) from its cervical vein by using 1/10 part by weight of 3.13% (w/v) sodium citrate, the sample was administered orally. At an appropriate time after the administration, the rat was intraperitoneally anesthetized (1 mg/kg) with Nembutal (50 mg/ml pentobarbital sodium, Abott Laboratories), followed by intravenous drip of 0.2 U/ml of tissue thromboplastin (Thromboplastin C plus, Dade Diagnostics of P. R. Inc.,) from the femoral vein for one minute at a rate of 2.5 to 3.0 ml/kg/min. The blood was collected (for measuring the number of platelets and anti-FXa activity) from the cervical vein 10 minutes after the intravenous drip and the blood was collected (for measuring TAT) from the cervical vein 20 minutes after the blood collection. The number of platelets, anti-FXa activity in the plasma and TAT concentration of each blood sample were measured. The number of the platelets was measured by an automatic cytometer, while the anti-FXa activity in the plasma was measured in a similar manner to that described in Test 4.

For the measurement of TAT (Thrombin-anti Thrombin = complex), EnzygnostR TAT micro kit (Boering Verke) was employed.

As a result of the oral administration of 30 mg/kg of the compound of Example B-36, apparent anti-FXa action in the plasma was recognized and a decrease in the number of the platelets and an increase in the TAT concentration were suppressed (the tissue thromboplastin was administered one hour after the administration of the sample).

Capability of Exploitation in Industry

The compound according to the present invention has peculiar and excellent FXa inhibitory action so that it is useful as a coagulation suppressor, or a preventive and/or remedy for thrombosis or embolism.

Use of the compound of the present invention as a pharmaceutical can therefore treat or prevent various diseases caused by a thrombus or embolus such as cerebral infarction, cerebral embolism, myocardial infarction, pulmonary infarction, pulmonary embolism, Buerger's disease, deep vein thrombosis, disseminated intravascular coagulation syndrome, thrombus formation after valve replacement, reocclusion after revascularization, formation of a thrombus upon extracorporeal circulation or coagulation upon blood collection.